A STUDY ON CLINICAL AND RADIOLOGICAL FEATURES OF NEUROCUTANEOUS SYNDROMES

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Madras Medical College

Chennai - 600 003

CERTIFICATE

This is to certify that the dissertation entitled**"A study on Clinical and Radiological Features of Neurocutaneous Syndromes"** is a bonafide original work of **Dr. T. Vijay**, in partial fulfillment of the requirements for **D.M. Branch - I (NEUROLOGY)** Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in AUGUST 2013, under our guidance and supervision.

Dr. C. Mutharasu M.D.,D.M.,
Professor of Neurology
Institute of Neurology
Madras Medical College
Chennai – 3

Dr. K. Deiveegan M.S., M.Ch.,
Professor and Head
Institute of Neurology
Madras Medical College
Chennai - 3

Dr. V. Kanagasabai M.D., Ph.D.,
Dean
Madras Medical College
Chennai – 3

DECLARATION

I hereby solemnly declare that this dissertation titled **"A study on Clinical and Radiological Features of Neurocutaneous Syndromes"** was done by me in Institute of Neurology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3, under the guidance and supervision of **Prof. Dr. C. Mutharasu. M.D., D.M.,** and **Prof. Dr. S. Balasubramanian. M.D.,D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of D.M Degree Branch I (NEUROLOGY).

Place: Chennai
Date: 25.03.13

Dr. T. Vijay
DM, Post Graduate
Institute of Neurology
Madras Medical College
Chennai - 3

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CONTENTS

INTRODUCTION

Neurocutaneous syndromes are a group of genetically determined heterogeneous disorders that manifest with developmental abnormalities of the skin and the nervous system. These disorders are believed to originate from the faulty differentiation of primitive ectoderm. The two most common neurocutaneous syndromes are Neurofibromatosis and Tuberous sclerosis. Sturge Weber syndrome, Ataxia telangiectasia and Epidermal naevus syndrome also occur commonly. Most of the other neurocutaneous syndromes are rare.

The cutaneous lesions usually appear at an early age and progress with time while neurological features usually manifest at a later age. The common neurological manifestations include learning disability, seizures, developmental delay and focal deficits but the expected neurological manifestation depends on the specific disease. Neuroimaging studies are helpful in the early diagnosis of neurological involvement. They also help to assess the extent of neurological involvement and to predict the prognosis.

Our study was designed to observe the manifestations in neurocutaneous syndromes at the time of diagnosis and to assess the extent of nervous system involvement using imaging studies.

AIM OF THE STUDY

1. To study the prevalence of various Neurocutaneous disorders.
2. To study the clinical manifestations of Neurocutaneous disorders.
3. To evaluate the incidence of neurological complications in patients with Neurocutaneous disorders.
4. To study the radiological features in Neurocutaneous disorders.

REVIEW OF LITERATURE

Neurocutaneous disorders are a group of genetic disorders that manifest with developmental lesions of the skin and the nervous system. Van der Hoeve, a Dutch ophthalmologist in the 19th century was the first to recognize the association of neurologic disease with cutaneous and retinal lesions. He coined the term phakomatosis (Greek phakos meaning spot, lens). He first included neurofibromatosis and turberous sclerosis but when he included Sturge Weber syndrome which does not present with hamartomas or phakomas, the term phakomatosis became inappropriate. The term neurocutaneous syndrome was introduced by Yakovlev and Guthrie in 1931 to describe these group of disorders. These disorders may be inherited or sporadic[1].

The neurocutaneous syndromes can be classified as follows[2]:

I. Autosomal dominant

1. Neurofibromatosis 1
2. Neurofibromatosis 2
3. Tuberous sclerosis
4. Von Hippel-Lindau disease
5. Hereditary hemorrhagic telangiectasia
6. Ehlers-Danlos syndrome type IV

II. Autosomal recessive

1. Ataxia-telangiectasia
2. Xeroderma Pigmentosum
3. Cerebrotendinous xanthoma
4. Pseudoxanthoma elasticum

III. X-linked dominant

1. Incontinentia pigmenti.
2. Focal Dermal hypoplasia

IV. X-linked Recessive

1. Fabry's disease
2. Menkes' syndrome

V. Sporadic

1. Sturge-Weber syndrome
2. Epidermal nevus
3. Progressive facial hemiatrophy
4. Hypomelanosis of Ito

NEUROFIBROMATOSIS

Neurofibromatosis is the most common neurocutaneous disorder. Two most common types are neurofibromatosis 1(NF1) and neurofibromatosis 2 (NF2)[3].

RICCARDI'S Classification System of Neurofibromatosis[4]

NF	Inheritance	Clinical Features
NF1	AD Gene 17q11.2	Café-au-lait spots (CALM), NF, axillary or inguinal freckles, Lisch nodules, bone changes, optic glioma.
NF2	AD, Gene 22q12.2	Bilateral vestibular schwannoma, multiple CNS Tumours – meningiomas, spinal astrocytomas, ependymomas, retinal hamatoma, cataracts.
NF3	AD (or) Sporadic	Features of NF1 and NF2 including some CALM, freckling, NF, CNS or paraspinal tumours, absence of vestibular shawannoma and lisch nodules.
NF4	Sporadic	Atypical ,a variant of type II
NF5	Sporadic / A.D	Segmental-one quadrant /one side of the body. It can be bilateral segmental NF with or without CALM
NF6	AD	Multiple CALM, but no neurofibroma. To diagnose this two generation should be affected.
NF7	Sporadic	Onset at end of 3rd decade or later. No Lisch nodules. Lesions appear after immunosuppressant.
NF8		NF not fitting into any of the above.

Neurofibromatosis 1

(Von Recklinghausen's disease/peripheral neurofibromatosis)

NF1 constitutes 96% of all cases of neurofibromatosis and the prevalence is 1:3,000.

Genetics

It is an autosomal dominant disease with variable expression and near complete penetrance. It is associated with NF1 gene mutation on chromosome 17q11.2. *NF1* gene is a tumor suppressor gene that codes for neurofibromin. Absence of neurofibromin leads to increased Ras activity and cell proliferation, resulting in neoplasms. Neurofibromin also regulate cyclic adenosine monophosphate levels.

Clinical Features

CUTANEOUS MANIFESTATIONS

1. Neurofibromas

Neurofibromas are hallmark findings of NF1 that often present at puberty and increase in number and size with age. They may be circumscribed (cutaneous or subcutaneous) or non circumscribed (plexiform). They are generally benign, but plexiform neurofibromas may undergo malignant transformation. They are commonly located near a spinal radicle.

Plexiform neurofibromas

Plexiform neurofibromas are specific to NF1 and are a major cause of morbidity. These lesions are irregular, thickened, non-circumscribed and disfiguring. They can envelop vital structures and can involve the orbit. Malignant peripheral nerve sheath tumors may develop from plexiform neurofibromas. 3% to 5% of NF1 patients develop malignant peripheral nerve sheath tumors[5]

2. Café-au-lait Macules (CALM)

They are sharply defined light brown macules and patches of varying sizes with smooth borders. They are found all over the body except scalp, palms and soles and eyebrows. CALM are the earliest to appear[6].

3. Freckling

Freckles are tan brown macules of 1-4 mm in diameter. Axillary freckling is called Crowe's sign. It is diagnostic when present in groin and axilla. Palmar freckling can also occur[7].

NEUROLOGICAL MANIFESTATIONS

Neurological features include cognitive deficits and learning disabilities[8]. There can be pain in specific nerve distribution due to presence of a neurofibroma. Visual complaints related to optic glioma

are common. Seizures may be due to intracranial tumors. Headaches may occur due to migraine or intracranial pressure. Progressive neurologic deficits can occur due to neurofibroma or other tumors. Moyamoya disease, intracranial aneurysms and migraine are other neurological features associated with NF1.

Nervous system tumours

Optic nerve gliomas are the most common CNS tumour in NF1. Low-grade pilocytic astrocytoma arising from optic nerve or chiasma may be an incidental finding or may present as progressive loss of vision and optic atrophy. Other tumours that can occur are parenchymal astrocytomas, meningiomas, pilocytic astrocytoma of the brainstem and cerebellum.

Ocular manifestations

Pigmented iris hamartomas otherwise called as Lish nodule occurs in 85to 90%. They are brownish translucent spots present bilaterally[9].

Skeletal Manifestations

They are sphenoid wing dysplasia, kyphoscoliosis[10], pseudoarthrosis, vertebral scalloping and macrocephaly. Congenital pseudo arthrosis is commonly seen in tibia or radius. Short stature due

to growth hormone deficiency has been reported. Thinning of cortex resulting in pathological fractures are common.

Pulmonary Change (10-20%)

Firbrosing alveolitis and interstitial fibrosis are the pulmonary changes associated with neurofibromatosis.

Gastro Intestinal (20%)

Constipation due to dysfunction of colonic musculature or colonic neurofibroma can occur. Recurrent Haemorrhages, obstruction or intussuception frequently involving the jejunum and stomach are the other manifestations.

Other features

Schwanoma, pheochromocytoma, neuroblastoma, ganglioglioma, Juvenile chronic myeloid leukemia and rhabdomyosarcoma are the other tumours associated tumours associated with neurofibromatosis. Other associated features are hypertension, proptosis, gynaecomastia, glaucoma and renal artery stenosis.

National institute of health Diagnostic Criteria for Neurofibromatosis 1[11]

Two or more of the following:

1. ≥6 café au lait spots
2. ≥2 neurofibromas of any type or ≥1 plexiformneurofibroma
3. Freckling (Crowe's sign) in axilla or groin
4. Optic glioma
5. ≥2 Lisch nodules (benign pigmented irishamartomas)
6. Distinctive bony lesion
7. First-degree relative with neurofibromatosis type 1

RADIOLOGICAL FEATURES IN NF 1

Approximately 60% to 78% of patients with NF1 have increased signal intensities within the basal ganglia, thalamus, brainstem, and cerebellum in T2-weighted MRIs. These areas are not routinely visible with CT. The origin and significance of these radiographic lesions are unclear. They are referred to as unidentified bright objects (UBOs).

CT Findings

Plain CT brain shows Sphenoid dysplasia with associated enlargement of middle cranial fossa and optic nerve glioma presenting as ipsilateral proptosis and enlarged optic nerves/chiasm. Contrast CT

shows enhancing visual pathway gliomas. CT angiogram shows vascular dysplasias and aneurysm.

MRI Findings

White matter (WM) lesions are variable intensity in T1 and hyperintense in T2. On contrast WM lesions usually don't enhance, Enhancement raises the concern of neoplasm. Plexiform lesions have variable enhancement. Excellent definition of plexiform and paraspinal neurofibromas are seen in STIR sequence. Optic nerve glioma are isointense or hyperintense. Best sequence for evaluation of visual pathway gliomas is T1 contrast. In MRS glioma have elevated choline peak. Spine imaging shows multiple level neurofibromas, dumbel tumour (characteristic of NF 1) and spinal cord compression.

NEUROFIBROMATOSIS TYPE 1- MYELIN VACUOLIZATION

Myelin vacuolization is previously known as hamartoma. They composed of dysplastic neurons and microcysts and are found in nearly 80% of cases. Common sites are basal ganglia especially globuspallidus, optic radiation, internal capsule, brain stem and cerebellar & cerebral peduncles[12].

In MRI, most areas of myelin vacuolization are isointense or hyperintense on T1WI, whereas most astrocytomas are hypointense.

In T2 and FLAIR images they are hyperintense and shows increased diffusion on diffusion weighted imaging (DWI). They may grow until the 10 years of age without any mass effect or contrast enhancement, after which it starts regressing. Magnetic resonance spectroscopy (MRS) shows minimally elevated choline and slight reduction in N-acetyl-aspartate (NAA) levels.

Radiography is useful in identifying sphenoid wing and occipital bone dysplasia and kyphoscoliosis.

NEUROFIBRAMATOSIS TYPE2

NF2 constitutes 3% of neurofibromatosis and the prevalence is 1:40,000.

Genetics

NF2 gene is a tumor suppressor gene located on chromosome 22q12. It codes for merlin expressed in adult Schwann cells, meningeal cells and lens.

Clinical manifestations

Symptoms often present in the teenage. Vestibular schwannoma is a nerve sheath tumour that typically occurs bilaterally. Clinical presentation often includes progressive hearing loss, tinnitus and imbalance.

Associated features

a. Spinal and cranial nerve (CN) schwannomas (CN V-XII)
b. Intracranial meningiomas
c. Spinal cord ependymomas, gliomas
d. Posterior subcapsular cataracts (85% of patients)
e. Retinal hamartomas
f. Café au lait spots (45% of patients)
g. Skin plaque like lesion (70% of patients)
h. Mononeuropathy (CN VII most common)
i. Seizures

Diagnostic Criteria

1. Bilateral eighth nerve tumor (shown by magnetic resonance imaging, computed tomography, or histological confirmation) or
2. A first-degree relative with neurofibromatosis type 2 and a unilateral eighth nerve tumour or
3. A first-degree relative with neurofibromatosis type 2 and any two of the following lesions: neurofibroma, meningioma, schwannoma, glioma, or juvenile posterior subcapsular lenticular opacity.

RADIOLOGY IN NF2

CT Findings

Plain CT shows cerebellopontine angle (CPA) mass with or without widened internal acoustic meatus (IAC) which is isodense to hyperdense with contrast enhancement. Meningioma is high density dural based mass with extensive calcifications in choroid plexus and cortical surface with contrast enhancement.

MRI Findings[13]

Schwannomas are hypointense to isointense on T1 and rarely cystic change can be seen on T2. Small intra canalicular lesions can be shown on high resolution T2WI. Diffuse homogeneous enhancement occurs. Vestibular schwannomas typically "bulge" into CPA cistern from IAC. MRS shows absent NAA peak.

Meningiomas are isointense to hypointense and occasional hyperintense foci from calcification with adjacent edema can be seen. Some meningiomas have restricted diffusion with diffuse enhancement of tumour. MRS shows absent NAA peak with or without lactate.

TUBEROUS SCLEROSIS (TSC)

Synonyms: EPILOIA, BOURNEVILLE'S DISEASE

TSC is as an autosomal dominant disorder with variable penetrance characterized by systemic hamartomas involving mostly the skin, nervous system, heart, eyes and kidneys.

Genetics

Two genes are responsible, TSC1 coding for hamartin at chromosome 9q34.3 and TSC2 coding for tuberin at chromosome16p13.3[14]. The clinical features of TSC1 and TSC2 overlap since the two gene products form a single functional unit that is an upstream modulator in the mTOR (mammalian target of rapamycin) signaling pathway. Both gene products down regulate small G-protein Ras-homologue enriched in brain (RHEB) activity in this pathway. TSC2 mutations appear more commonly than TSC1 in patients with subependymal nodules, mental retardation, renal angiomyolipomas and retinal phakomas.

Cutaneous Features

The cutaneous lesions of TSC include hypomelanotic macules, shagreen patch, ungual fibromas and facial angiofibromas.

1Ash leaf spots: Hypomelanotic macules occur in up to 90% of affected individuals. The lesions usually are present at birth but may be seen in the newborn only with an ultraviolet light. Other pigmentary abnormalities include confetti lesions (areas with stippled hypo pigmentation, typically on the extremities) and poliosis (a white patch or forelock) of the scalp, hair, or eyelids. Hypomelanotic macules are common in normals[15].

2. Facial angiofibromas (adenoma sebaceum): consist of vascular and connective tissue elements. Although considered specific for TSC, they are found in only three-fourths of affected individuals. The lesions typically become apparent during the preschool years as a few small red macules on the malar region. They gradually become papular, larger and more numerous, sometimes extending down the naso labial folds and chin. Laser therapy is useful prior to puberty[16].

3. Shagreen patch: is most often found on the back or flank area and is usually considered specific for TSC. It is an irregularly shaped, slightly raised or textured skin lesion. Only 20% to 30% of patients with TSC have one patch, which may not be seen in young children.

4. ***Ungual fibromas*** are nodular or fleshy lesions that arise adjacent to (periungual) or underneath (subungual) the nails. These can occur as a

single lesion after trauma in normal individuals. Ungual fibromas occur in only 15% to 20% of patients with TSC, more likely in adolescents or adults[17].

Neurological Features

The predominant neurological manifestations of TSC are mental retardation, seizures, and behavioral abnormalities. It is due to abnormal neuronal migration along radial glial fibers and abnormal proliferation of glial elements. Neuropathological lesions of TSC include subependymal nodules (SENs) seen in 98% of patients, cortical and subcortical hamartomas (75%), areas of focal cortical hypoplasia and heterotopic gray matter[18].

Seizures

Seizures of various types occur in 80% to 90% of patients[19]. Most develop during the first year of postpartum, which is an indicator for autism and poor cognitive development. One third of children with TSC develop infantile spasms .Children with infantile spasms have more cortical lesions. Vigabatrin has been a more effective treatment option than adrenocorticotropin hormone (ACTH). Resective epilepsy surgery is a consideration in individuals with seizures localizing to a single tuber[20]. Most patients with mental retardation have epilepsy, but many have seizures with normal intelligence. The number of

subependymal lesions does not correlate with the clinical severity of TSC.

In addition to intellectual disability, many children with TSC have serious behavioral disorders. Autistic behavior, hyperkinesis, aggressiveness, and frank psychosis sometimes occur, either as isolated problems or in combination with epilepsy or intellectual deficit.

Subependymal nodules (SENs)

SENs commonly arise from germinal matrix progenitors in the caudothalamic groove near the foramen of Monro. These lesions can grow over time, but usually only into adolescence, after which time they calcify. These remain asymptomatic unless they enlarge and transform into subependymal giant-cell astrocytomas (SEGAs) seen in 15% of cases[21].

Cortical tubers

Tubers frequently extend from the ventricle wall to the cortical surface. Histology of these areas demonstrates disorganized cortical lamination and underlying abnormal myelination. Calcinosis is frequently present. Abnormal astrocytes of focal cortical dysplasias are termed balloon cells or giant cells for their abundant cytoplasm.

Renal manifestations (80%)

The common renal manifestations reported are renal angiomyolipoma, aneurysmal dilatation of renal arteries, renal artery stenosis and polycystic kidneys (12%). Hypertension in children with TSC can be due to renal parenchymal lesions like angiomyolipomas and cyst. Malignant epitheloid renal angiomyolipoma in a patient with TSC has been reported. This is related to a contiguous gene syndrome because mutations span both the TSC2 gene and the adjacent polycystic kidney disease gene (PKD).

Cardiac Manifestation

Rhabdomyomas of the heart are common . 80% of all children presenting with Rhabdomyoma have TSC. Wolff-Parkinson-White syndrome and ventricular arrhythmias have also been reported.

Diagnostic Criteria for Tuberous Sclerosis Complex[22]

Major Features

1. Facial angiofibromas or forehead plaque
2. Nontraumaticungual or periungual fibroma
3. Hypomelanotic macules
4. Shagreen patch
5. Multiple retinal nodular hamartomas
6. Cortical tuber

7. Subependymal nodule
8. Subependymal giant-cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

Minor Features

1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white-matter radial migration lines
5. Gingival fibromas
6. Non renal hamartoma
7. Retinal achromic patch
8. Confetti skin lesions
9. Multiple renal cysts

- Definite tuberous sclerosis complex: either 2 major features or1 major feature plus 2 minor features.
- Probable tuberous sclerosis complex: 1 major plus 1 minor feature.
- Possible tuberous sclerosis complex: either 1 major feature or 2 or more minor features.

CT Findings

In Plain CT sub ependymal nodule (SENs) are seen along caudo thalamic groove. Calcification is seen in 50%. Low density tubers are seen in cortical/sub cortical region. SEGA is evidenced by ventriculomegaly and contrast enhancement[23].

MRI Findings

SEN enhancement is more visible on MRI than on CT and 30-80% enhance. In FLAIR, Streaky linear or wedge-shaped hyper intensities along radial migration lines from ventricle to cortex called radial bands are commonly seen in frontal then parietal region. Axial flair MRI better visualize tubers and SEN. SEGA is diagnosed by contrast enhancement and choline peak in MRS. PET scan shows reduced glucose metabolism in lateral temporal gyri in TSC with autism patients. Rhabdomyomas are identifiable as early as 20 weeks gestation.

STURGE-WEBER SYNDROME

(Encephalotrigeminal angiomatosis)

It is a sporadic condition characterized by leptomeningeal angiomatosis and ipsilateral facial cutaneous vascular malformation called port-wine nevus, usually in distribution of ophthalmic division of trigeminal nerve. Prevalence is 1:50,000.

Pathology

Symptoms are generally related to leptomeningeal angiomatosis, a low-flow vascular malformation. They are 85% unilateral and are usually located in posterior parietal and occipital regions. They do not cause subarachnoid haemorrhage.

Clinical Manifestations

Port-wine nevus

A cutaneous vascular malformation distributed in ophthalmic division of Cranial nerve V over forehead and upper eyelid or periorbital area usually unilateral, bilateral rarely.

Seizures

Occur in up to 75% to 90% of patients with Sturge-Weber syndrome by the age of 3 years. Mean age at onset is 6 months. Onset of seizures occurs during first year of life in 75% of patients, before 2 years in 86%, and before 5 years in 95%. Typically focal motor seizures occur but secondary generalized tonic clonic seizures may also develop. Other types of seizures like atonic, tonic, myoclonic, or infantile spasms can also occur. Associated features are developmental delay, emotional and behavioural problems and mental retardation.

Focal deficits

Hemiparesis (25% to 60%) occurs contra lateral to leptomeningeal angiomatosis due to chronic hypoxia[24]. Hemianopia can occur in up to 40% . Vascular steal phenomenon may develop around angioma, resulting in progressive calcification, gliosis, and atrophy.

Developmental disorders

Developmental disorders may occur in 50% to 75% of cases. It is more common in patients with bilateral angiomatosis.

Ophthalmic features

Glaucoma can occur in eye ipsilateral to port-wine nevus, highest likelihood when both the upper and lower eyelid are involved. Other associated features are buphthalmos, choroidal hemangioma of eye.

Subtypes

1. Type I: both facial and leptomeningeal angiomas; may have glaucoma.
2. Type II: facial angioma alone; may have glaucoma.
3. Type III: isolated leptomeningeal angiomatosis; usually no glaucoma.

CT Findings

Plain CT shows progressive calcification of gyral or subcortical white matter and atrophy over parieto occipital region. In contrast CT, serpentine leptomeningeal enhancement is seen.

MRI Findings

In early part atrophy of white matter, later white and gray matter atrophy. Gradient echo shows tram-track gyral calcifications with pial enhancement on contrast. MRV shows lack of superficial cortical veins and reduced flow in transverse sinuses and jugular veins with prominent deep collateral veins. PET scan shows progressive glucose hypometabolism and SPECT scan shows hypo perfusion. Angiography shows paucity of normal cortical veins, extensive medullary and deep collaterals[25].

Radiography of the skull shows Tram-track calcification.

ATAXIA TELANGIECTASIA

ATM gene is located on chromosome 11q22-q23. ATM protein is located in the nucleus and has a role in cell cycle control and mitogenic signal transduction.

Clinical Features

1. Telangiectasias are found in conjunctiva, nose, ear, neck, antecubital fossa, and popliteal fossa. Oculocutaneous telangiectasias usually occur after the onset of ataxia around 4 to 6 years of age. Usual age of onset is between 1 and 2 years.
2. Ataxia predominantly truncal is usually the first symptom, then appendicular ataxia and dysarthria occurs. Ophthalmic features include jerky pursuit movements with loss of optokinetic nystagmus and limitation of upgaze, slow saccades and oculomotor apraxia. Rare associated neurological features are choreoathetosis, dystonia, large-fiber sensory (demyelinating) peripheral neuropathy, reduced or absent deep tendon reflexes, very rarely extensor plantar responses. Progressive distal muscle atrophy may occur later[26].
3. Predisposition to neoplasia, mainly leukemia or B-cell lymphoma occurs before age of 20 years. Sinopulmonary infections are the other associated features.

Increased level of alpha feto protein, decreased serum levels of IgA, IgE, IgG, (IgG2) and increased levels of IgM may be found. Pathologically Cerebellar (vermis) atrophy, cell loss in inferior olivary nucleus, dentate nucleus, Purkinje cells, and granule cells,

degenerative changes in the spinal cord affecting the posterior and lateral columns and anterior horn cell may occur. Imaging shows cerebellar vermian atrophy[27].

GIANT CONGENITAL MELANOCYTIC NAEVUS (NEUROCUTANEOUS MELANOSIS)

It is a congenital disorder of melanotic cell development and migration characterized by cutaneous melanocytic nevi and a high risk of developing benign or malignant melanocytic tumours of the central nervous system. Accumulation of melanotic cells occurs in arachnoid and piamater, amygdala, cerebellum, thalamus, frontal lobes and basal brain.

Clinical Manifestations

1. 65% of patients have giant congenital melanocytic nevi (more than 20cm) present at birth over head and scalp. Presence of naevi over the back implies an increased likelihood of developing neurologic symptoms. Satellite nevi may occur around giant nevus (80%). Risk of developing melanoma is 5% to 15%.
2. Neurological manifestations include leptomeningeal melanosis, intracranial melanoma and intracerebral or subarachnoid haemorrhage. Hydrocephalus may occur as a result of

accumulation of melanotic cells at basal subarachnoid cisterns. Other neurological features are seizures (44%), papilledema (31%), headaches (30%), mental retardation (18%), cranial nerve palsies, malformation of vertebral column, spinal cord, cerebrum and Dandy-Walker malformation. Leptomeningeal proliferation affecting spinal cord results in myelopathy and cauda equina syndrome[28].

3. Other associated neoplasms are embryonal rhabdomyosarcoma, malignant schwannoma in retroperitoneum and liposarcoma.

Diagnostic Criteria

1. Multiple (≥3) congenital nevi in association with meningeal melanosis or melanoma(in infant ≥ 9 cm on scalp or ≥ 6 cm over body and in adult ≥ 20 cm) .
2. Absence of malignant melanoma in any organ (including skin) other than central nervous system.

Imaging

Brain MRI may demonstrate T1 shortening in presence of melanin. Gadolinium enhancement of leptomeninges correlates with presence of melanin in leptomeninges. If lesions are suspected follow up with serial MRI is recommended.

HYPOMELANOSIS OF ITO

It is the third most frequent neurocutaneous disease exceeded by NF1 and TSC. It is a sporadic disease most common on chromosomes18, 12, and X.

Clinical Features

1. Skin: Macular hypopigmented whorls and patches with irregular borders and white lines of Blaschko type is the common presenting feature which occur within first 2 years of life in 90% of patients. Lesionsdoes not correlate with severity of disease. Other types of cutaneous lesions are nevus marmorata, angiomatous nevi and Mongolian blue spot.
2. Neurological features include mental retardation, autism, seizure, strabismus and nystagmus.
3. Other features are dental hamartomatous tumors, scoliosis, finger and toe anomalies, corneal opacification and cataracts.

Brain imaging shows atrophy and hemimegalencephaly (50%), cerebellar hypoplasia and agyria, pachygyria[29].

FABRY'S DISEASE

(ANGIOKERATOMACORPORIS DIFFUSUM)

It is a X-linked recessive lysosomal storage disease resulting from the deficiency of α-galactosidase. *GAL* gene is localized to

chromosome Xq22. Sphingolipid accumulation occurs in vascular endothelial cells, smooth muscle cells, sweat gland cells, macrophages, central neurons, gastrointestinal ganglionic neurons, cardiac muscle, astrocytes, meningeal cells and autonomic ganglion cells resulting in clinical manifestations.

Clinical Manifestations

1. May begin as early as 4 years. Mean age of onset is 10 years. Skin manifestations include angiokeratoma which are hyperkeratotic areas of dilated blood vessels, typically purple-black in color. They are most commonly seen over the "swim trunk" region.
2. Neurological manifestations include pain crises (characterised by acute, episodic, neurogenic pain triggered by stress, heat, fatigue, exercise) and acroparesthesia resulting from small-fiber peripheral neuropathy[30]. Rarely small-vessel ischemic strokes can also occur.
3. Other features are corneal opacity, progressive renal failure, hypertension, myocardial infarction, valvulopathy, cardiomyopathy and depression.

Fabry's disease is diagnosed by low or absent α-galactosidase A enzyme level in plasma, serum, leukocytes, or cultured fibroblasts. Skin, kidney and conjuctival biopsy are also helpful in the diagnosis.

VON HIPPEL-LINDAU DISEASE

It is an autosomal dominant disease characterized by hemangioblastomas of central nervous system and retina and renal cell carcinomas. Other associated features are pheochromocytomas, pancreatic isletcell tumors, endolymphatic sac tumors of middle ear, neuroendocrine tumors of pancreas and cystadenomas of epididymis and broad ligament. VonHippel-Lindau (*VHL*) gene is located on chromosome 3p26-p255.

Diagnostic Criteria[31]

1. Family history and the finding of a single retinal or Cerebellar hemangioblastoma, pheochromocytoma, or renal cell carcinoma.
2. If no definite family history of VHL disease, two retinal or cerebellar hemangioblastomas or one hemangioblastoma plus one visceral tumor.

Types

Type I. VHL without pheochromocytoma (most common type)

Type II. VHL with pheochromocytoma

Imaging finding

Hemangioblastoma are detected by imaging. Common CNS sites are cerebellar hemisphere, followed by spinal cord usually cervical or thoracic region.

HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Syn: OSLER WEBER RENDU DISEASE

It is an autosomal dominant disease characterized by mucocutaneous telangiectasias in multiple organs. Usually onset of illness occurs before 40 years of age. There are 2 sub types. HHT 1 and HHT 2. Type 1 is usually associated with pulmonary involvement.

Clinical Manifestations

1. Mucocutaneous telangiectasias: common locations are nasal cavity, oral cavity, lips and fingers.
2. Neurological manifestations include cerebral abscess, stroke, or transient ischemic attack (TIA) due to paradoxical shunting, cerebral and spinal arteriovenous malformations, cerebral aneurysms, cavernous angiomas and migraine headache[32].

Criteria for Diagnosis of Hereditary Hemorrhagic Telangiectasia

1. Epistaxis: recurrent nose bleeds
2. Telangiectasias: in lips, oral cavity, fingers, nose

3. Visceral lesions: Gastrointestinal telangiectasias, pulmonary and hepatic arteriovenous malformations, spinal and cerebral vascular malformations.
4. Family history of first-degree relative with hereditary hemorrhagic telangiectasia
    1. Definite: three criteria are present
    2. Possible: two criteria are present
    3. Unlikely: fewer than two criteria present.

Neuro imaging shows flow voids, with or without hemorrhage, mass effect, edema, gliosis. GRE is useful in detecting micro-hemorrhages.

XERODERMA PIGMENTOSUM

It is an autosomal recessive disorder that presents with extreme photosensitivity of skin and eyes and premature cutaneous aging. The defect is in the genes involved in nucleotide excision repair mechanisms. Higher incidence is reported in Israel, Japan and Egypt.

Clinical Manifestations

1. Photosensitivity, erythema and blistering starts between 1to2 years of age in 50% of patients, by 4 years in 75% of patients and by 15 years in 95% of patients. They may later develop basal cell carcinoma[33].

2. Eyes are affected in 80% with the median age of 4 years. Telangiectasias, ectropion, entropion and keratitis are the common ophthalmic features.
3. Neurologic manifestations include mental retardation, ataxia, spasticity, abnormal ocular motility, sensory neural deafness, seizures and axonal neuropathy[34]. Rarely DeSanctis-Cacchione syndrome (progressive neurologic degeneration) develops in 20% of patients. Carcinoma is the most common cause of death followed by infection. MRI shows cortical atrophy.

EPIDERMAL NEVUS SYNDROME (Schimmelpenning's syndrome)

It May be sporadic or autosomal dominant with the incidence of 1:1,000 live births. Male and female are equally affected.

Clinical Manifestations

1. **Epidermal nevi**

They are typically linear, do not cross midline and follow the lines of Blaschko. Head and neck are the most common sites of occurrence. It can involve anus, mouth and genitalia.

2. **Neurological manifestations**

Occur in 50% of patients. Seizures, mental retardation and rarely spastic hemiparesis can occur. Structural abnormalities include

hemiatrophy, hemimegalencephaly, agenesis of corpus callosum and hamartoma[35].

3. Eyelid involvement, choristomas[36], kyphoscoliosis and enamel hypoplasia are the other abnormalities that can occur.

Neuroimaging shows calcifications and angiography shows arteriovenous malformations.

MENKES' SYNDROME (KINKY HAIR DISEASE)

It is a X-linked recessive lethal disorder resulting from maldistribution of body copper. Responsible gene is *MNK* gene on chromosome Xq13 that encodes for copper-transporting membrane ATPase which is expressed in all tissues except liver. Pathological features are degeneration of cortical gray matter, with neuronal loss and gliosis and loss of Purkinje cells in cerebellum.

Clinical Manifestations

1. Most common initial symptoms are delayed development and seizures.
2. Hypothermia, hypotonia, hypoglycemia and failure to thrive are the symptoms seen in neonates.
3. Hair becomes colourless and friable. Trichorrhexis nodosa may occur.

4. Other associated findings are osteoporosis, hydronephrosis and blindness. Subdural hematoma and respiratory failure are late manifestations. Majority die before the age of 2years due to infections and cerebral haemorrhage[37].

Diagnosis is by low copper and ceruloplasmin levels. Neonatal diagnosis can be made by copper uptake studies in cultured fibroblasts.

MRI shows diffuse cortical atrophy and impaired myelination.

CEREBROTENDINOUS XANTHOMATOSIS

It is an autosomal recessive disorder that affects the brain and tendons. The defective gene is located on chromosome 2q33. Impaired hepatic conversion of cholesterol to cholic and chenodeoxycholic acids leads to accumulation of cholesterol and cholestenol in tissues. This results in xanthomatous lesions in the Cerebellum adjacent to dentate nucleus, basalganglia, brainstem and spinal cord[38].

Clinical features

1. Tendonxanthomas are seldom seen before 20 years. They are commonly found over achilles tendon.
2. Mental retardation, pyramidal and cerebellar signs are the neurological manifestations.

3. Other features are premature atherosclerosis, osteoporosis, repeated fractures, cataracts, chronic diarrhea and pulmonary insufficiency.
4. Early diagnosis and treatment can prevent neurologic complications. Presence of two of four clinical hallmarks should prompt metabolic screening which may reveal increased plasma and bile cholestanol levels and increased urinary bile alcohol glucuronides associated with decreased biliary concentration of chenodeoxycholic acid. Brain imaging shows cerebral and cerebellar atrophy.

INCONTINENTIA PIGMENTI
(BLOCHSULZBERGER SYNDROME)

It is a X-linked dominant disorder with mutation of NEMO/IKKγ gene located on Xq28. This gene is involved in expression of multiple genes protecting cells against apoptosis.

Clinical Manifestations

1. Skin features: skin lesions appear at or shortly after birth and evolve over time. Skin manifestation occurs in four stages.

Stages of Incontinentia Pigmenti

Stage 1: Bullous stage (birth to first 8 weeks of life)

Stage 2: Verrucous stage (arises as stage 1 begins to resolve)

Stage 3: Hyper pigmentation stage (6 months into adulthood)

Stage 4: Atrophic stage (does not occur in all patients).

2. Neurologic features are mental retardation (15%), seizures, infantile spasms (13%) and microcephaly (5%)[39].

3.20% may have severe vision abnormalities like retinal or ocular lesions vitreous hemorrhage, retinal detachment, strabismus and conjunctival pigmentation.

4. Absent teeth and poor enamel quality, skull deformities, scoliosis, clubfoot and syndactyly are the other features.

Diffuse atrophy, hypoplasia of corpus callosum and ventricular dilatation are the imaging findings that may be present.

ENCEPHALOCRANIOCUTANEOUS SYNDROME

(HEBERLAND SYNDROME)

It is a sporadic disorder characterized by neurological, skin and eye abnormalities. It usually presents in infancy to childhood. Skin features are lipoma, polyps, alopecia and nail changes. Neurological manifestations are mental retardation, seizures, macrocephaly, hemiplegia, quadriplegia and spastic paraplegia. Eye features are chorioretinal abnormalities and micropthalmos. Facial dysmorphism is not uncommon. Unilateral cerebral hemispheric atrophy ipsilateral to

scalp lipoma is noted. MRI detects intracranial (1C) lipomas and spinal lipomas mostly at cervicothoracic than lumbar region. Hemispheric atrophy, ventriculomegaly due to volume loss, leptomeningeal lipomatosis and polymicrogyria are the other features detected by imaging[40].

PROGRESSIVE FACIAL HEMIATROPHY (PARRY-ROMBERG SYNDROME)

Typically presents in first or second decade. Female male ratio is1.5:1. Cause is unknown. Proposed theories include infection, trigeminal neuritis, scleroderma and cervical sympathetic loss. Sometimes it may begin after trauma.

Clinical Manifestations

Progressive hemifacial atrophy in the distribution of cranial nerve V and linear scleroderma of forehead called en coup DeSabre are the classical findings. Central nervous system features include trigeminal neuralgia, migraine, seizures, hemianaesthesia, hemianopia and ipsilateral Horner syndrome. Loss of hair and vitiligo are associated features[41]. MRI shows ipsilateral corpus callosum infarction, sub cortical white matter changes, ipsilateral leptomeningeal enhancement and calcification and ipsilateral atrophy[42].

Ehlers-Danlos Syndrome Type IV

It is an autosomal dominant disorder that occurs due to mutation of*COL3A1* gene on chromosome 2 which encodes for type III procollagen synthesis. Deficiency of collagen type III, which is a major component of distensible tissues including arteries and veins, results in fragmentation of arterial internal elastic membrane, fibrosis of arterial wall and microscopic ruptures between media and adventitia.

Clinical presentation

1. Easy bruising, thin translucent skin, thin nose, hollow cheeks, reduced adipose tissue and skin hyperextensibility.
2. Small joint hypermobility and tendon rupture
3. spontaneous pneumothorax and early varicose veins .
4. Neurological features include optic atrophy, sensory neural hearing loss, cerebellar ataxia and neuropathy[43].

   It is diagnosed by fibroblast culture to detect procollagen III molecules. Neuro imaging shows intra cranial aneurysm and cerebral atrophy.

Cerebrovascular Complications

1. Carotid-cavernous fistula
2. Spontaneous arterial dissection
3. Intracranial aneurysm formation

MATERIALS AND METHODS

The study was done at Madras institute of Neurology, Rajiv Gandhi Government General Hospital, Chennai for a period of 24 months, from January 2011 to December 2012. Hundred patients with symptoms and signs pertaining to neurocutaneous syndromes were included in the study.

Basic demographic data like age, sex and educational qualification were noted. A detailed history was elicited including history of present and past illness; family history and consanguinity. General examination and a detailed systemic examination were done in all patients to look for any associated systemic abnormalities.

A detailed history pertaining to neurological symptoms was elicited and a thorough examination of the central nervous system was done in all patients. Assessment of IQ was done. The cutaneous findings were noted and a dermatologist opinion was obtained. Eye examination, ear and dental examinations were done and opinion obtained in relevant cases.

The following investigations were done in all patients:

1. Complete hemogram
2. Liver function test
3. Renal function test
4. Blood Sugar
5. Serum Lipid Profile
6. X Ray
7. ECG
8. Ultrasound abdomen
9. EEG
10. CT/MRI

Nerve conduction study was done in relevant cases. The radiological findings were noted and analyzed in all patients.

The data thus obtained was compiled, tabulated and analyzed.

OBSERVATION AND RESULTS

Total number of new patients who attended the neurology OPD at Government General Hospital during the period between January 2011 to December 2012 were 32,168. Among them 100 patients (0.3%) were identified with symptoms and signs pertaining to neurocutaneous disorders. The various neurocutaneous disorders that were observed in our study are as follows in order of frequency.

1. Neurofibromatosis	-	66
2. Tuberous sclerosis	-	18
3. Sturge Weber syndrome	-	4
4. Ataxia telangiectasia	-	3
5. Epidermal naevus syndrome	-	2
6. Giant congenital melanocytic naevus	-	2
7. Xeroderma pigmentosum	-	1
8. EhlerDanlos syndrome type IV	-	1
9. Hypomelanosis of Ito	-	1
10. Incontinentia Pigmenti	-	1
11. Hereditary hemifacial atrophy	-	1

In our study the most common neurocutaneous disorder observed was Neurofibromatosis followed by Tuberous sclerosis and

Sturge Weber syndrome. Seizures were the most common neurological manifestation noted in these disorders followed by learning disability and mental retardation.

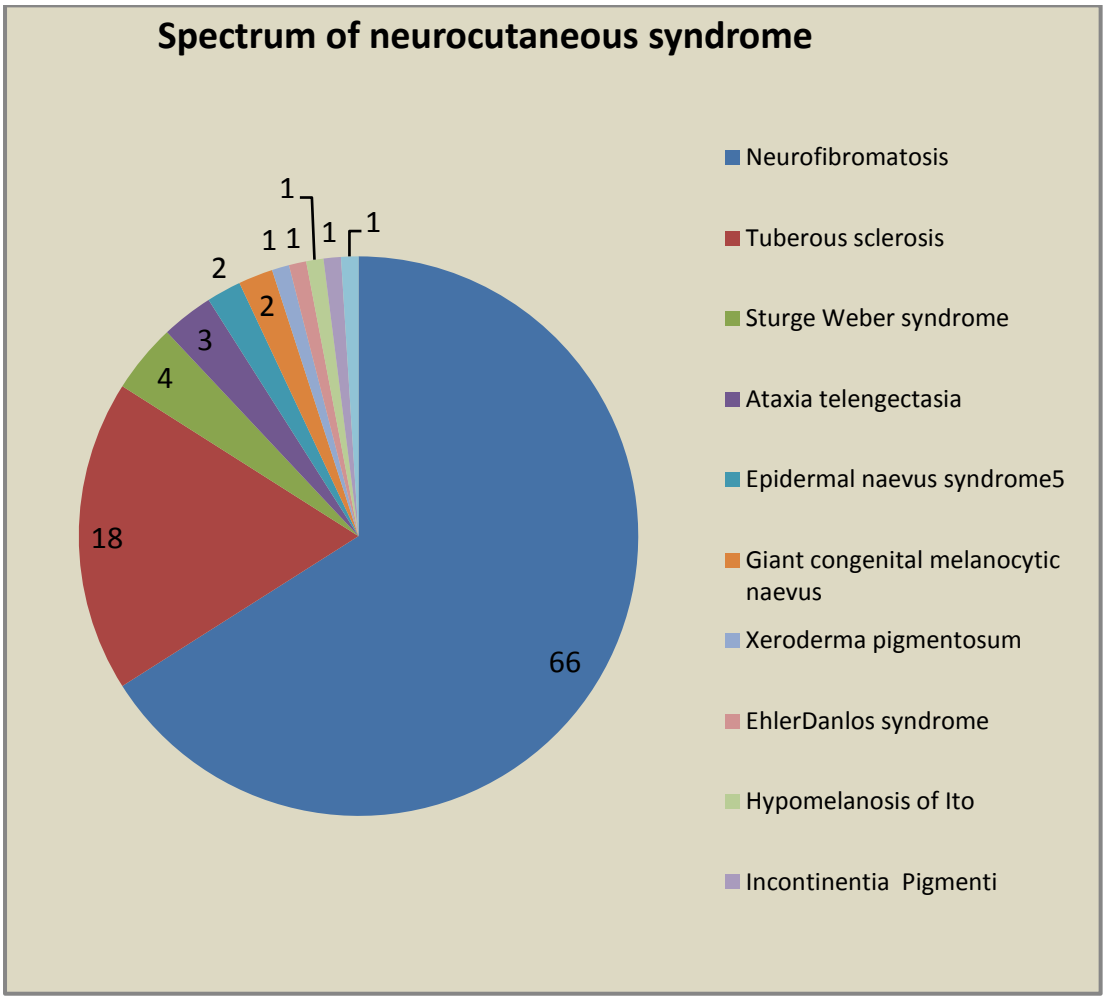

Figure: 1

NEUROFIBROMATOSIS (NF)

66 cases of neurofibromatosis were observed in our study. Of these, 59 cases (89.3%) had NFI, 3 cases (4.5%) had NFII, 2 cases (3.03%) had NF V and 2 cases (3.03%) had NF VI.

TABLE 1

Types of neurofibromatosis observed in our study

Type of Neurofibromatosis	No. of cases	%
NF I	59	89.3
NF II	3	4.5
NF V	2	3
NF VI	2	3

Age and sex distribution: The age group of patients with neurofibroma ranged from 1 to 55 years with the mean age of 28 years.

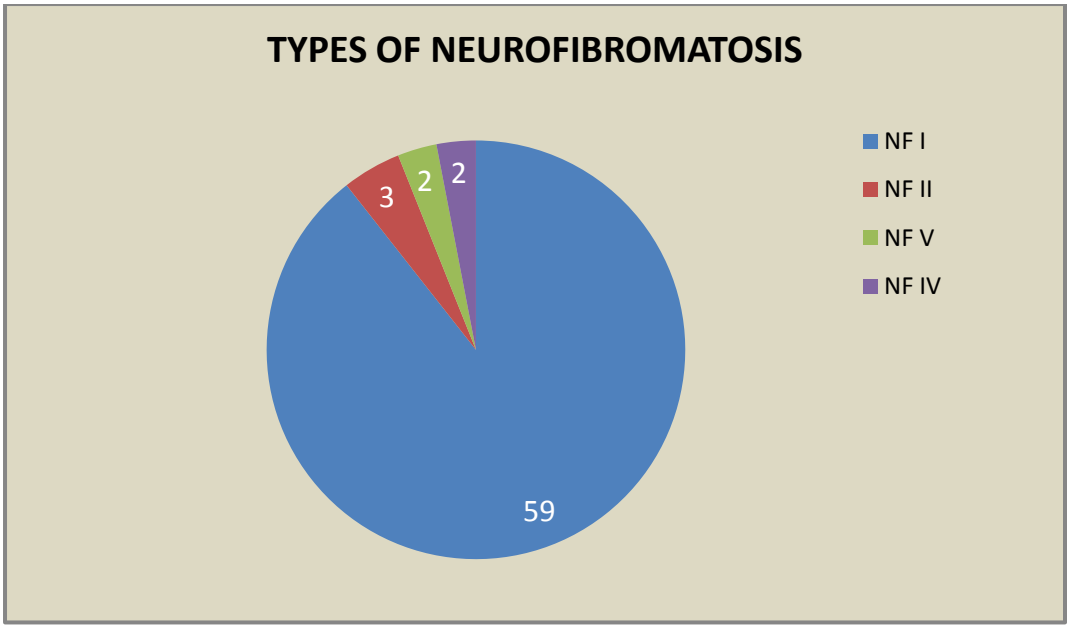

Figure 2

TABLE-2

The Age and Sex Distribution among Patients with NF (N=66)

Age	No. of Cases	M	F
< 10 yrs	3	2	1
11 – 20 yrs	25	14	11
21 – 30 yrs	19	10	9
31 – 40 yrs	13	8	5
41 – 50 yrs	3	1	2
Above 50 yrs	3	2	1
Total	**66**	**37**	**29**

Family History: Neurofibromatosis was observed among the family members in 18 cases (27.2%).

Cutaneous manifestations: 61 patients (92.4%) had mollusca fibrosa (neurofibroma) lesions. Plexiform neurofibromatosis was observed in 3 patients (5%) of which one patient presented with plexiform neurofibromatosis in the lower limb. Café au lait macules were seen in 57 patients (86%). Freckling in the palms, axillary and inguinal regions was noted in 52 patients (78%). One male patient had excessive freckling over the face. It was noted from the history that café au lait macules were the earliest cutaneous marker to appear and the number of neufibroma lesions increased at puberty.

Neurological Manifestations*:* 13 patients (19.6%) with NFI had neurological symptoms of which 3 patients (5%) presented with seizures. Two patients had generalised tonic clonic seizures and one had right focal seizures with secondary generalisation. Five patients (7.5%) had mental retardation, 6 patients (9%) had learning difficulties, 2 patients (3%) had quadriparesis and 1 patient (1.5%) had paraparesis. One patient (1.5%) had optic nerve glioma and presented with loss of vision.

All the three NF2 patients presented with hearing loss. One case of NF2 with bilateral acoustic schwannoma presented with features of raised intracranial tension.

TABLE - 3

Neurological manifestation in neurofibromatosis

Neurological manifestation	No. of Patients
Seizures	3
Learning disability	6
Mental retardation	5
Quadriparesis	2
Paraparesis	1
Vision loss	1
Sensory neural deafness (NF 2)	3

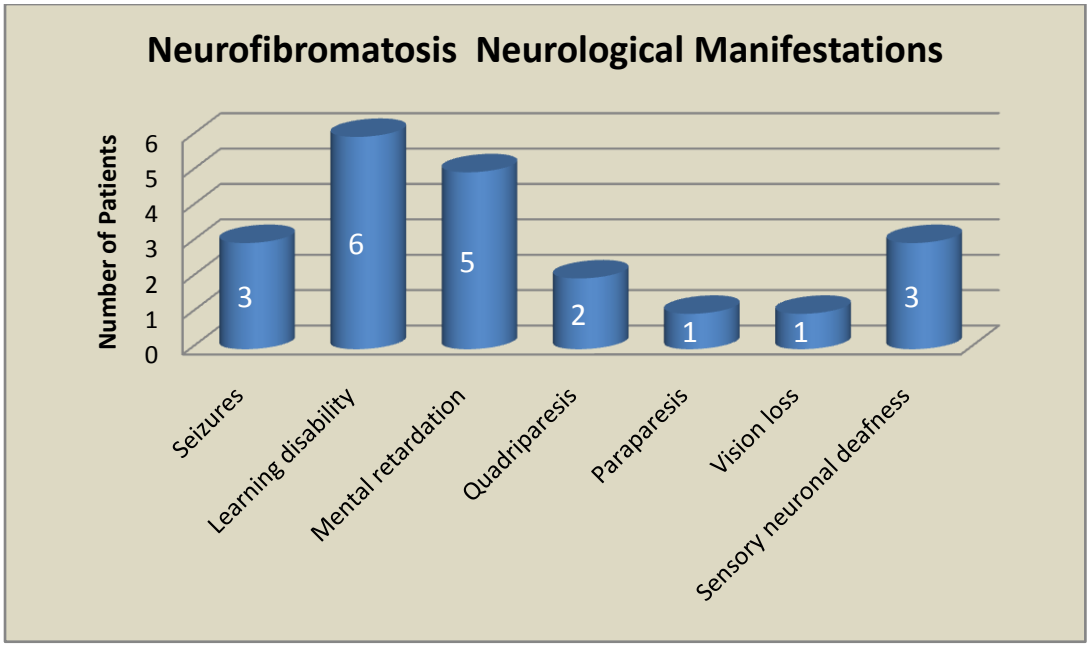

Figure: 3

EEG findings: Among the 3 patients who presented with seizures, 2 patients showed epileptiform activity in EEG.

Ophthalmic manifestations: 49(74%) patients had lisch nodules in both eyes.

Bony abnormalities: 9 patients (13.6%) had bony abnormalities of which 5 had kyphoscoliosis (7.5%), 2 had facial asymmetry (3%) and 2 had pseudoarthrosis of tibia (3%).

TABLE-4

Systemic manifestations observed in patients with neurofibromatosis

Systemic Manifestations	No. of Patients
Bony abnormalities	
Kyphoscoliosis	5
Facial asymmetry	2
Pseudoarthrosis of tibia	2
Ophthalmic Manifestations	
Lisch nodules	49

Imaging studies

Radiological abnormalities were present in 21 patients (31.8%). MRI T2 weighted images showed small multiple high signal intensity areas called unidentified bright objects (UBOs) in 12 patients (20%) with NF1. One patient had optic nerve glioma and none of the patients had parenchymal glioma. Hamartoma in thalamus and parietal cortex were present in two patients. One patient who presented with quadriparesis showed spinal cord intra dural extramedullary compression at cervical level. The other patient with quadriparesis showed multiple level compressions. Imaging of another patient who presented with paraparesis showed compression at thoracic level with lateral extension through the nerve root forming dumb bell tumour.

TABLE -5

Neuro imaging in Neurofibromatosis

S. No	Type of neurofibroma	Imaging finding	No. of patients
1	NF1	UBO	12
2	NF1	Optic nerve glioma	1
3	NF1	Hamartoma	2
4	NF1	Spinal cord compression	3
5	NF2	Acoustic neuroma	3

MRI in all the 3 patients with NF2 showed acoustic neuroma. One patient had multiple schwannoma, meningioma and ependymoma (Multiple inherited Schwannoma, Meningioma and Ependymoma - MISME syndrome).

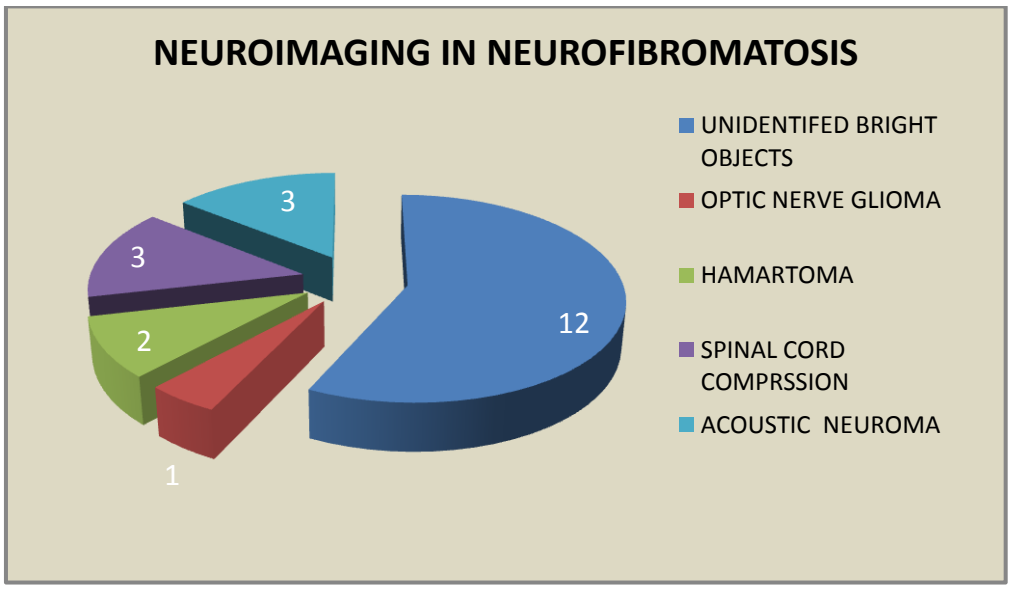

Figure: 4

TUBEROUS SCLEROSIS (TSC)

Eighteen patients were diagnosed with tuberous sclerosis of whom 6 were male and 12 were female. The age of these patients ranged from 4yearsto 38 years – the mean age being 21 years.

TABLE -6

The age and sex distribution in tuberous sclerosis complex (n=18)

Age	No. of Case	M	F
Less than 10 yrs	3	1	2
11 – 20 yrs	9	3	6
21 – 30 yrs	4	1	3
31 – 40 yrs	2	1	1
TOTAL	**18**	**6**	**12**

***Family history*:**

Two families were documented with manifestations of tuberous sclerosis in three generations.

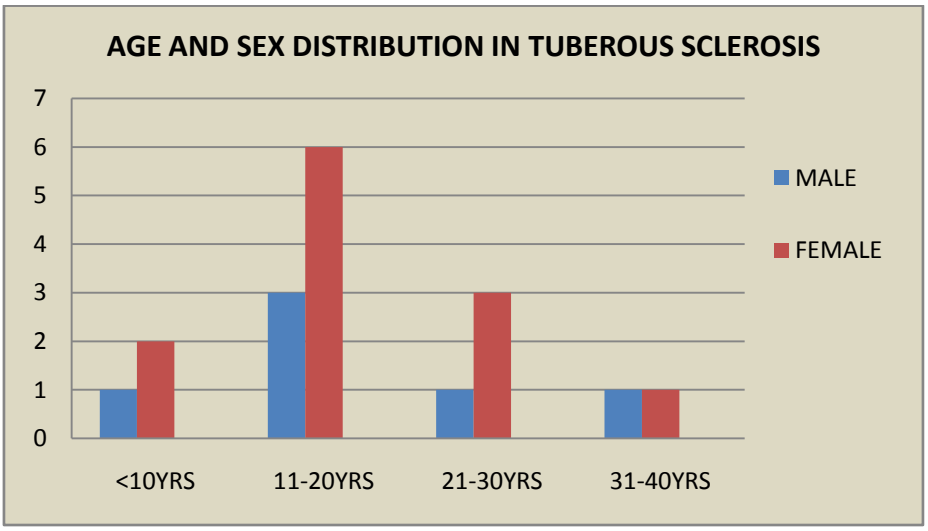

Figure: 5

TABLE - 7

Cutaneous findings in patients with tuberous sclerosis

Cutaneous Marker	No of Patients (Total = 18)
Angio fibroma	18(100%)
Ash leaf macules	16(85%)
Shagreen patch	12(75%)
Molluscum pendulum	3(35%)
Forehead plaque	4(20%)
Koenen'stumour	5(28%)
CALM	3(16%)
Confetti macules	2(11%)
Gingival fibroma	1(5%)
Enamel pits	10(60%)

Angio fibroma was the most common cutaneous finding followed by Ash leaf macules and Shagreen patch. Shagreen patch was frequently seen in the lumbosacral region.

Neurological manifestations:

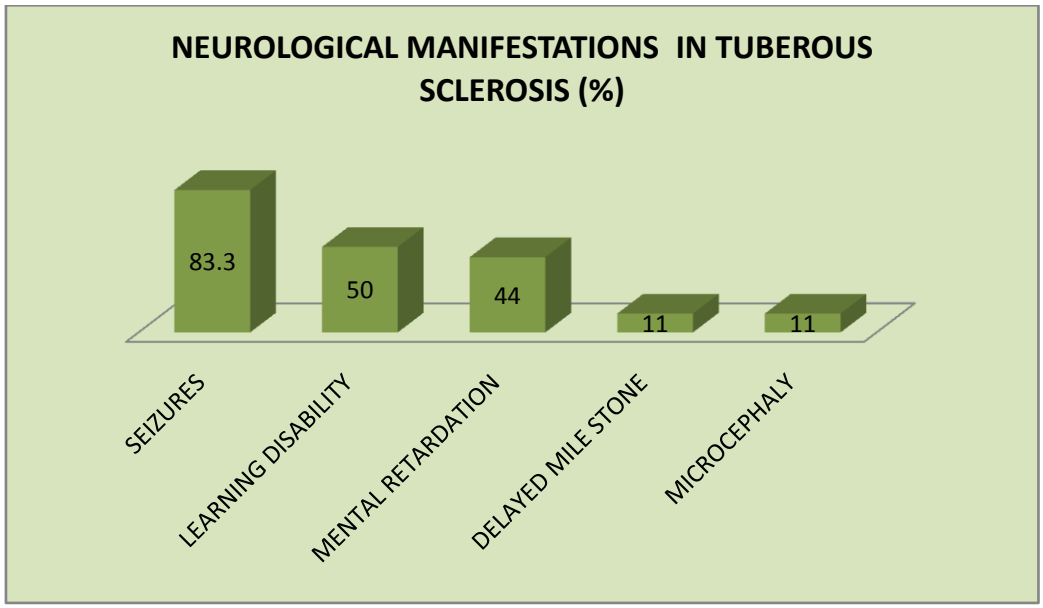

Figure: 6

Seizure was the most common neurological symptom noted in patients with tuberous sclerosis. Fifteen patients (83.3%) had seizures of which 9 patients had generalized tonic clonic seizures, 3 patients had focal seizures with secondary generalization and 3 patients had multiple seizure type. Of the fifteen patients with seizures 12 patients (80%) had intractable seizures. Eight patients (44.4%) had mental retardation and 2 patients (11%) had history of delayed mile stones. Learning disability was noted in 9(50%) patients. Microcephaly was noted in 2 patients (11%).

TABLE - 8

Neurological manifestations in tuberous sclerosis

S. No	Symptom	No. of patients
1.	Seizures	15(83.3%
2.	Learning disability	9(50%)
3.	Mental retardation	8(44.4%)
4.	Delayed mile stones	2(11%)
5.	Microcephaly	2(11%)

EEG findings: Abnormal findings in EEG were present in 6 patients of whom 4 patients showed spike and slow waves, and 2 patients showed bilateral diffuse slow waves.

Imaging studies:

Neuroimaging revealed abnormality in 7 patients (38%). Subependymal nodules were noted on the walls of lateral ventricle in 3 patients (16.6%). Cortical tubers were noted in 3 patients (16.6%), all in frontal lobe which were not enhancing with contrast. Sub ependymal giant cell astrocytoma (SEGA) was present in one patient (5.5%).

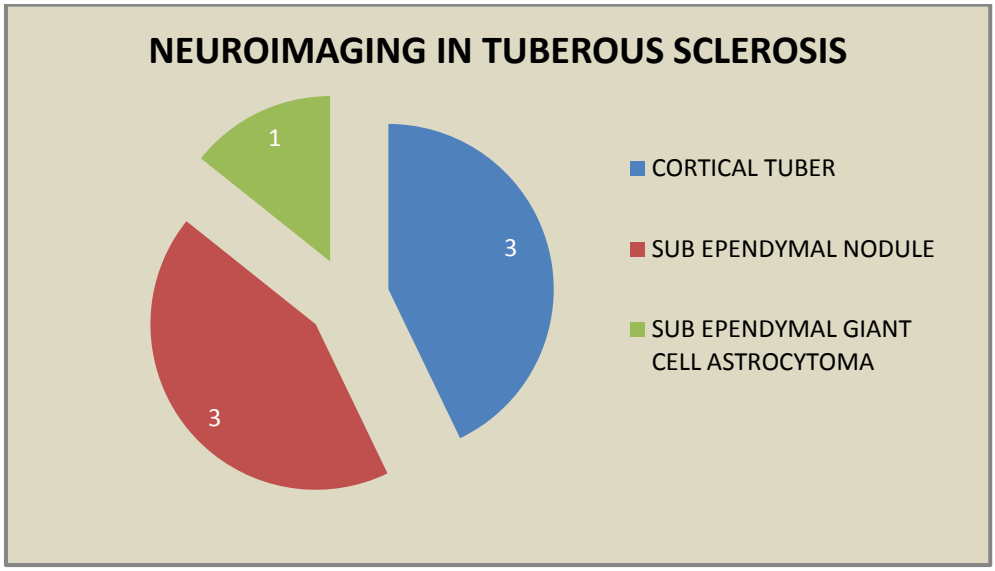

Figure: 7

Other findings:

Ultrasonogram of abdomen revealed renal angiomyolipoma in two patients. Echocardiogram of one patient showed rhabdomyoma of heart.

STURGE WEBER SYNDROME

Four patients were identified to have Sturge Weber syndrome of whom three were female and one was male. All the patients denied family history or consanguinity. All the four patients presented with portwine stain over the face. Three patients had unilateral portwine stain while one patient had bilateral portwine stain. In addition to portwine stain, conjunctival congestion, prominent blood vessels over the upper and lower eyelids and glaucoma were also noted in the patient with bilateral portwine stain.

TABLE - 9

Clinical spectrum in Sturge Weber syndrome

No of patients	4
Sex Distribution	M – 1, F – 3
Portwine stain	3 – Unilateral; 1 – Bilateral
Other features	Conjunctival congestion, prominent blood vessels over the upper & lower eyelids and glaucoma
Neurological Manifestation	Seizures
Neuroimaging	Calcification over the parietooccipital region with atrophy

Among the four patients, three patients presented with seizures and their EEG showed focal epileptiform spikes. One female patient presented at the age of thirteen years with low IQ, intractable seizures, and squint. One patient presented at the age of 60 years with seizures and haemangioma of lower lip.

Imaging of these patients showed serpiginous calcification and atrophy over the parietooccipital region with. Gradient echo showed blooming.

ATAXIA TELANGIECTASIA

TABLE - 10

Clinical Spectrum in Ataxia telangiectasia

No of patients	**3**
Sex Distribution	M – 1, F – 2
Telangiectasia	All patients (seen at conjunctiva)
Neurological Manifestation	Ataxia in all 3 patients. One patient had oculomotor apraxia, peripheral neuropathy, mental retardation and seizures also.
Neuroimaging	Cerebellar atrophy

Three patients were diagnosed with ataxia telangiectasia. Two patients, an eight years old female child and a thirteen years old male child were siblings from the same family. All the three patients had telangiectasia in the conjunctiva. One patient had telangiectasia over the nose also. Truncal ataxia, nystagmus, dysarthria and recurrent respiratory infections were noted in all the three patients. All had absent deep tendon reflex. In addition to the above findings, a thirteen years old patient presented with low IQ, generalised tonic clonic seizures, sensory neuropathy, oculomotor apraxia, severe limb and truncal ataxia. He also had impaired GTT and epileptiform activity in EEG. MRI of this patient showed severe atrophy of cerebellar hemispheres and vermis. MRI of the other two patients showed only vermian atrophy.

Other rare Neurocutaneous Syndromes

Few uncommon neurocutaneous syndromes observed in our study and their clinical features and imaging findings are tabulated (Table 11).

TABLE - 11

Other rare Neurocutaneous Syndromes

5555	No. Of patients	Neurological Manifestion	Cutaneous Manifestion	Imaging
Epidermal naevus syndrome	2	Seizure – 1 Headache -1	Epidermal Naevus	Normal
Giant congenital melanocytic naevus	2	Seizure – 1 Headache -1	Giant Naevus	Normal
Xeroderma Pigmentosum	1	Optic atrophy Deafness, Mental retardation	Photophobia, Freckles, xerosis	Diffuse cortical atrophy
EhlerDanlos syndrome	1	Optic atrophy Deafness	Hyperextensible Skin and joints	Normal
Hypomelanosis of Ito	1	Seizure Mental retardation	Hypopigmentation along Blaschkow lines	Pachygyria
Incontinentia Pigmenti	1	Seizure	Marble cake pigmentation	Cortical atrophy
Hereditary hemifacial atrophy	1	Seizure	Atrophy of face	Ipsilateral Hemispheric atrophy

TABLE 12

Summary of neurological manifestations in Neurocutaneous Syndrome

Neurocutaneous Syndromes	Neurological manifestations						
	Seizure	**Learning Disability**	**Mental Retardation**	**Ataxia**	**Weakness**	**Deafness**	**Blindness**
Neurofibromatosis (n - 66)	3	6	5	-	3	3	1
Tuberous sclerosis (n - 18)	15	9	8	-	-	-	-
Sturge Weber syndrome (n - 4)	3	1	1	-	-	-	-
Ataxia telengectasia (n - 3)	1	1	1	3	1	-	-
Epidermal naevus syndrome (n - 2)	1	-	-	-	-	-	-
Giant congenital melanocytic naevus (n - 2)	1	-	-	-	-	-	-
Xeroderma pigmentosum (n - 1)	-	1	1	-	-	1	1
EhlerDanlos syndrome (n - 1)	-	-	-	-	-	1	1
Hypomelanosis of Ito (n - 1)	1	1	1	-	-	-	-
Incontinentia Pigmenti (n – 1)	1	-	-	-	-	-	-
Hereditary hemifacial atrophy (n - 1)	1	-	-	-	-	-	-

DISCUSSION

Neurocutaneous disorders are a group of genetic disorders characterized by congenital dysplastic abnormalities involving the skin and the nervous system. Skin lesions usually appear at an early age while neurological features usually present at a later age. Neuro imaging studies help to assess the extent of neurological involvement and to predict the prognosis. With this background we studied 100 cases of neurocutaneous disorders and analyzed the neurological manifestations and the radiological findings.

The most common neurocutaneous disorder observed in our study was neurofibromatosis (66%) followed by tuberous sclerosis (18%) and Sturge Weber syndrome (4%). Other rare neurocutaneous disorders like ataxia telengectasia (3%), Giant congenital melanocytic naevi (2%), Epidermal naevus syndrome (2%), Xeroderma pigmentosum (1%), Incontinentia Pigmenti (1%), Hypomelanosis of Ito (1%), Ehler Danlos Syndrome (1%) and Hereditary Hemifacial atrophy (1%) were also observed.

Seizures, learning disability and mental retardation were the most common neurological symptoms noted in our study. The most common neurocutaneous disorder that presented with seizures was

Tuberous Sclerosis (83.3%) followed by Sturge Weber Syndrome (75%). Seizures were also noted with high frequency in other less common disorders like Ataxia telengectasia, Giant congenital melanocytic naevi, Epidermal naevus syndrome, Hypomelanosis of Ito, Heritary hemifacial atrophy and Incontinentia pigmenti also. Neurofibromatosis was the most common disorder observed in our study but the prevalence of seizures in neurofibromatosis was low. These findings coincide with the study by Prakash Kotagal et al[44].

NEUROFIBROMATOSIS

Neurofibromatosis type 1 was the most common type of neurofibromatosis noted in our study and accounts for 89.3% of neurofibromatosis cases. This is closer to the incidence noted in the series of Husan SM et al[45]where they have documented 90% incidence. The incidence of NF1 was higher in our study compared to the study by Sandipandhar et al[46]in which the incidence of NF1 was only 60%. The incidence of NF2 in our study was 4.5%. Few cases of rare NF variants were also observed. Two cases (3%) each of NF V and NF VI were noted in our study. Crowe FW et al[47] considered NF VI to be a rare variant.

In our study male sex (56%) was predominantly affected which is in contrast with the study by Jennifer R. Kam et al[48]who showed

equal male female ratio. The most frequent age group affected was 11-20 years.

In our study, Mollusca fibrosa (92.4%) was the most common cutaneous finding followed by Cafe au lait macules (86%) and freckling(78%).Increase in number of lesions at puberty which was noted in our study was also noted by Friedmann JM Riccardi et al[49]. Café u lait macules were the earliest marker to occur in our study. This coincides with the study by Crow and Schull et al[50,51]. The incidence of café u lait macules was higher in our study compared to the study by Neil Gold Berg et al[52] in which Café au lait macules were noted in 69% of cases. Plexiform neurofibromatosis was observed in 5% of cases in our study as opposed to the 30% incidence noted in the Wallenstein et al study[53]. Axillary freckling was noted in 78% of cases which was closer to the incidence of 70% noted in the study by Crowe FW et al[51] .

Lisch nodules were observed in 74% of patients as opposed to Fliieler et al study which showed 95% occurence.[54] Kyphoscoliosis was noted in 7.5% of patients which was higher than the 2% incidence noted in the study by Riccardi VM et al[55]. Pseudoarthrosis of tibia was seen in 3% of cases as opposed to AJ Kanwar et al [56] study which showed 13% incidence.

Neurological manifestations were noted in 19.6% of neurofibromatosis cases which coincides with the study by Kaufmann et al[57]. Among the neurological manifestations seizure was noted in 5% of cases while 10% of cases were found to have seizures in the study by Cramer et al[58]. Mental retardation occurred in 7.5% of cases as opposed to the study of Allanson JE et al[59.].Learning difficulty was noted in 9% of cases which was lesser than the 30 – 70% incidence in the North Kn et al study[60].Compressive myelopathy occurred in 5% of cases in our study as opposed to the study of Leonard et al[61] in which 1% had compressive myelopathy.

In our study 100% of NF2 patients presented with acoustic neuroma which was much higher than the incidence of 30% noted in the study by Loveneret al[62].

Radiological findings were present in 31.8% of Neurofibromatosis patients. This was closer to that of Hsiesh HY et al study[63] in which radiological findings were present in 35% of cases. The most common finding in MRI T2 weighted imaging was Unidentified bright objects (UBO) noted in 20% of cases which coincides with the observation of DeBella et al[64]. Optic nerve glioma was present in 1.5% of patients. These findings coincide with the study by Szudek J et al[65]. In our study imaging showed spinal cord

compression in 5% of cases as opposed to the study by J R Leonard et al[61] which noted spinal cord root compression in 1% of cases.

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TUBEROUS SCLEROSIS

Tuberous Sclerosis (18%) was the second most common neurocutaneous disorder observed in our study next to neuro fibromatosis. The common age group of presentation was 10-20 years. The mean age of presentation in our study was 21 years while G. Raghu Rama Rao et al[66] study noted a mean age of 16 years. In our study, family history was present in 10% of patients. This was lesser compared to H. Northrup et al[67] study who observed positive family history in 30% of their cases. Our study noted a female preponderance as opposed to Rabindrnath Nambi et al[68]study which showed an equal sex incidence.

Angiofibroma of the face was the most common cutaneous finding which was present in all patients in our study. This was consistent with Gomez MR et al[69]study which showed 95% incidence. Ash leaf macule was observed in 85% of cases as opposed to 100% in Jimbow K et al [70]study. Shagreen patch was found in lumbosacral region frequently which is consistent with the report of Tsao H et al.[71.]Shagreen patch was observed in 75% of cases as opposed to 50% reported by Harris stith et al[72 .]

Koenens tumour was noted in 28% of cases which was higher than the 15% incidence noted by Joswiak et al[31]study. Among the neurological manifestations, seizures were found in 83%of cases in contrast to the Satish chandra et al[73] study where they have observed seizures in only 53% of their cases. Seizures were refractory to treatment in most of the cases. In our study we noted mental retardation in 44.4% of cases which was closer to the 40% incidence noted by Raghu Rama Rao et al.[66.] Microcephaly with seizures was noted in 11% of cases in our study and this was consistent with Chandra PS et al[74] study.

Neuroimaging :

Subependymal nodules were noted in 16.6% of cases as opposed to Curatolo p et al[75] study which noted 50% incidence. Cortical tuber was noted in 16.6% in contrast to Rupa Radhakrishnan et al[76]study where they noted 80% incidence. Sub ependymal giant cell astrocytoma was noted in only 5.5% of patients in our study in contrast to 26% of patients in Morimoto et al series[77]. Renal angiomyolipoma was detected in 10% in contrast to 60% reported in many literatures.

STURGE WEBER SYNDROME

In our study, 4% of patients were diagnosed to have Sturge Weber syndrome with unilateral port wine stain in 75% of cases and bilateral portwine stain in 25% of cases. This coincides with Tallman B et al study[78]. There was a female preponderance. 75% of patients presented with seizures which was similar to the findings of Sujansky E et al[79] study where seizures was observed in 75 to 90% of their cases. The seizures were refractory to medications as shown in Tallman B et al study[78]. EEG showed focal epileptiform spike discharges which coincides with the Brennei RP et alstudy[80].In neuro imaging Leptomeningeal angiomatosis, the hall mark of sturge weber syndrome was observed in 75% of our patients which is consistent with Griffith et al study[81].

ATAXIA TELANGIECTASIA

In our study 3% of patients were found to have ataxia telangiectasia. 100% presented with oculcutaneous telangiectasias and 66% had a positive family history. These findings coincide with Sedwick R etalstudy[82].All patients had ataxia, dysarthria and recurrent respiratory infections which were similar to the findings in Boder E et al study[83]. In neuro imaging 100% had vermian atrophy which coincides with the study by Ottonello C et al[84]. One patient showed sensory neuropathy and impaired GTT as described in literatures.

EPIDERMAL NAEVUS SYNDROME

2% of patients in our study had epidermal naevus syndrome. One patient had migraine headache. One patient (50%) had seizures which correlated with the study of Gurecki PJ et al[85]. None of our patients had other neurological abnormalities like facial hemiatrophy, mental retardation and neuronal migration disorder as shown in Rizzo R et al study.[86] Neuro imaging studies of these patients were normal.

GIANT CONGENITAL MELANOCYTIC NAEVUS

In our study 2% of patients presented with giant congenital melanocytic naevus. Hypertrichosis was seen in 100% of the cases which is consistent with that described in literature[87]. One patient had associated seizures and café- u-lait macule in accordance with the study of Zvulunova et al[88]. Another patient had migraine. Both the patients had normal neuro imaging studies as opposed to the study by Chien JC et al [89]which showed leptomeningeal thickening and atrophy.

XERODERMA PIGMENTOSUM

In our study one female patient had Xeroderma Pigmentosum. Photophobia and freckles were the common presentations. Conjuctival pigmentation, congestion and loss of vision were present. These findings coincide with that of AK Dubey et al study[90]. Mild cognitive impairement was present and neuro imaging of this patient revealed diffuse cortical atrophy.

EHLER DANLOS SYNDROME TYPE IV

We noted one patient with EhlerDanlos syndrome type IV. Hyper extensibility of all joints, easy bruising, thin translucent skin, hollow cheeks and reduced adipose tissue over the face were the clinical findings in the patient. Clinical examination revealed bilateral optic atophy with hearing loss. These findings were noted in the AB Tally et al study[91]also.

HYPOMELANOSIS OF ITO

In our study we noted a case of Hypomelanosis of Ito with delayed motor and language milestones, learning disability and seizures. Whorled linear hypopigmented lesions were present along Blaschko lines over face, trunk and upper limb. These findings were noted in Pescual et al series[92] also. Neuroimaging showed diffuse cerebral atrophy and pachygyria which coincides with the study of steiner et al[93].

INCONTINENTIA PIGMENTI

A ten months old female baby with history of blistering in the neonatal period was diagnosed to have incontinentia pigmenti. The baby had brownish hyperpigmentation over the axilla and groin with a marble cake appearance. The baby presented with seizures. All these

findings coincide with the study of Smal Hadji-Rabia et al[94]. Neuroimaging showed diffuse cortical atrophy.

PROGRESSIVE FACIAL HEMIATROPHY (PARRY-ROMBERG SYNDROME)

In our study we noted one patient with Parry Romberg syndrome. His unpleasing facial appearance with bone and soft tissue atrophy correlates with the findings of the study by Stone et al[95]. Neuroimaging showed ipsilateral hemispheric atrophy which coincides with the findings of Corry et al[96].

CONCLUSION

1. The most common Neurocutaneous syndrome observed in our study was Neurofibromatosis (66%) followed by Tuberous sclerosis (18%).
2. The most common neurological manifestation noted in our study was seizure.
3. Among the neurofibromatosis, NF I accounted for the maximum number of cases. Rare variants like NF5 and NF6 were also observed.
4. Most common cutaneous marker in our series was neurofibroma.
5. Learning disability, seizures, mental retardation and quadriparesis were the common neurological manifestations observed in neurofibromatosis.
6. The most common symptomatology in tuberous sclerosis was adenoma sebaceum. Intractable seizures was the most common neurological feature.
7. Among the imaging findings, unidentified bright objects (UBO) were the most common MRI finding in NF 1 and Cortical tuber and sub ependymal nodules were the common imaging findings in tuberous sclerosis.

8. Sturge Weber syndrome (4%) presented with portwine stain and intractable seizures. Parietooccipital calcification and cortical atrophy were seen in neuro imaging.
9. Other rare neurocutaneous syndromes observed in our study were Ataxia Telangiectasia, Epidermal naevus syndrome, Ehlers Danlos Syndrome type IV, Parry Romberg syndrome, Xeroderma pigmentosum, Incontinentia pigmenti, Hypo-melanosis of Ito and Congenital melanocytic naevus.

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ABBREVIATIONS

TSC	**:**	TUBEROUS SCLEROSIS
NF	**:**	NEUROFIBROMATSIS
MRI	**:**	MAGNETIC RESONANACE IMAGING
CT	**:**	COMPUTED TOMOGRAPHY
MRS	**:**	MAGNETIC RESONANCE SPECTROSCOPY
NAA	**:**	N- ACETYL ASPARTATE
GRE	**:**	GRADIENT ECHO
EEG	**:**	ELECTRO ENCHEPHALOGRAM

PROFORMA

Serial No: OP No.:

Name: Address:

Age:

Sex:

Occupation:

If Child, informant:

Complaints:

H/o Presenting Illness:

Onset:

Duration of skin lesions:

Site of initial lesion:

Size of the lesion:

Number:

Progression – Evolution:

Sites affected:

H/o pain over the lesion:

H/o photosensitivity:

H/o Blisters:

H/o Dry Skin:

H/o Pigmentary disturbance:

H/o Alopecia:

H/o Loss of nail:

H/o Convulsions:

H/o Headache:

H/o Milestones development:

H/o Mental retardation:

H/o Neuropsychiatry manifestation:

H/o Self mutilation:

H/o Visual disturbance:

H/o Photophobia:

H/o Night blindness:

H/o Hearing impairment:

H/o Hoarseness of voice:

H/o Dyspnoea:

H/o Gynaecomastia :

H/o Sexual development:

H/o Muscle weakness:

H/o Growth retardation:

H/o Bone involvement:

H/o Teeth anomalies:

H/o Urinary symptoms;

H/o Nausea / Vomiting:

H/o Abdominal pain:

H/o Haematemesis:

H/o Constipation / diarrhea:

H/o Loss of appetite:

Past History:

Treatment History:

Personal History:

Family History:

GENERAL EXAMINATION:

Built:

Nourishment:

Orientation:

Pallor:

Clubbing:

Cyanosis:

Jaundice:

Pedal edema:

Lymhadenopathy:

Pulse:

BP:

SYSTEMIC EXAMINATION

CNS:

Higher mental functions:

Cranial nerves examination:

Spino motor system examination:

Bulk: Tone

Power Reflex

Gait:

Sensory system examination:

Cerebellum examination:

Extra pyramidal system:

Autonomic nervous system:

Spine and cranium:

OTHER SYSTEM EXAMINATION:

CVS:

RS:

ABDOMEN:

DERMATOLOGICAL EXAMINATION:

Morphology:

Number:

Site:

Size:

Distribution:

Shape:

Colour:

Tenderness:

Consistency:

Compressibility:

Surface:

Lesions Like:

1. Neurofibroma
2. Café au lait spots
3. Freckles
4. Lentigens
5. Angiofibroma
6. Shagreen patch
7. Ash leaf macule
8. Hypopigmented macules
9. Naevi
10. Palmar pits
11. White forelock
12. Synophrys

INVESTIGATIONS

Complete haemogram

Blood sugar Lipid profile

LFT

RFT

Xray skull

USG ABDOMEN

NCS

EEG

CT Scan brain

MRI Brain

OPINIONS:

Dermatology opinion

Psychiatrist opinion

Neuro surgeon opinion

Opthalmologist opinion

Cardiologist opinion

DIAGNOSIS:

PATIENT CONSENT FORM

Study Details : Clinical and Radiological features in Neuro Cutaneous Syndromes

Study Centre : Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai - 600 003.

Patient may check (□) these boxes:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. □

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. □

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulartory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. □

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. □

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study.

Signature / Thumb impression:

Patient Name and Address: Place: Date:

Signature of Investigator:

Study Investigator's Name: Place: Date:

MASTER CHART 1: NEUROFIBROMATOSIS

SNO	AGE	SEX	FH	NF	CALM	FRC	PX	MR	SZ	LD	PARESIS	PE	HEAR	LISCH	BONY	EEG	CT			MRI		
																		UBO	ONG	SPINAL TUMOUR	ACOUSTIC NEUROMA	HAMARTOMA
1	28	M	1	2	1	1	1	1	1	1	2	2	2	1	1	AB	N	P	A	A	A	A
2	18	M	1	1	1	1	2	1	1	1	2	2	2	1	2	AB	N	P	A	A	A	A
3	13	F	1	1	1	1	2	2	1	1	2	2	2	1	2	N	N	P	A	A	A	A
4	51	M	2	1	1	1	2	2	2	2	1	2	2	1	1	N	N	A	A	P	A	A
5	48	M	2	1	1	1	2	2	2	2	1	2	2	1	1	N	N	A	A	P	A	A
6	53	F	2	1	1	1	2	2	2	2	1	2	2	1	1	N	N	A	A	P	A	A
7	22	F	1	2	2	2	2	2	2	2	2	1	1	2	2	N	AB	A	A	A	P	A
8	26	F	1	2	2	2	2	2	2	2	2	2	1	2	2	N	AB	A	A	A	P	A
9	31	M	1	2	2	2	2	2	2	2	2	2	1	2	2	N	AB	A	A	A	P	A
10	54	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	P	A	A	A
11	7	M	1	1	1	1	2	2	2	2	2	2	2	1	1	N	N	P	A	A	A	P
12	9	M	1	1	1	1	2	2	2	2	2	2	2	1	1	N	N	P	A	A	A	P
13	38	M	2	1	1	1	2	2	2	2	2	2	2	1	1	N	N	A	A	A	A	A
14	39	M	2	1	1	1	2	2	2	2	2	2	2	1	1	N	N	A	A	A	A	A
15	36	M	2	1	1	1	2	2	2	2	2	2	2	1	1	N	N	A	A	A	A	A
16	32	M	2	1	2	1	1	1	2	2	2	2	2	1	2	N	N	P	A	A	A	A
17	34	M	2	1	1	1	1	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
18	31	F	2	1	1	1	2	1	2	2	2	2	2	1	2	N	N	P	A	A	A	A
19	34	F	2	1	1	1	2	1	2	2	2	2	2	1	2	N	N	P	A	A	A	A
20	43	F	1	2	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
21	29	F	1	2	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
22	44	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A

MASTER CHART 1: NEUROFIBROMATOSIS

SNO	AGE	SEX	FH	NF	CALM	FRC	PX	MR	SZ	LD	PARESIS	PE	HEAR	LISCH	BONY	EEG	CT			MRI		
																		UBO	ONG	SPINAL TUMOUR	ACOUSTIC NEUROMA	HAMARTOMA
23	27	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
24	28	M	2	1	1	2	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
25	14	M	2	1	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
26	22	M	2	1	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
27	16	M	2	1	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
28	26	F	2	1	1	2	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
29	22	F	2	1	1	2	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
30	6	F	2	1	2	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
31	31	M	2	1	2	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
32	38	M	2	1	2	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
33	18	M	2	1	2	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
34	34	F	2	1	2	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
35	21	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
36	20	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
37	17	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
38	26	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
39	19	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
40	29	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
41	18	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
42	23	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
43	14	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
44	17	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A

MASTER CHART 1: NEUROFIBROMATOSIS

SNO	AGE	SEX	FH	NF	CALM	FRC	PX	MR	SZ	LD	PARESIS	PE	HEAR	LISCH	BONY	EEG	CT			MRI		
																		UBO	ONG	SPINAL TUMOUR	ACOUSTIC NEUROMA	HAMARTOMA
45	14	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
46	22	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
47	16	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
48	27	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
49	14	F	2	1	1	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
50	26	F	2	1	1	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
51	22	M	2	1	1	1	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
52	14	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
53	15	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
54	18	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
55	18	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
56	11	F	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
57	14	M	2	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
58	11	M	2	1	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
59	26	M	2	1	1	2	2	2	2	2	2	2	2	2	2	N	N	A	A	A	A	A
60	15	M	2	1	1	2	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
61	36	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
62	37	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	P	A	A	A	A
63	13	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
64	22	M	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	P	A	A	A	A
65	16	F	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A
66	18	M	1	1	1	1	2	2	2	2	2	2	2	1	2	N	N	A	A	A	A	A

MASTER CHART 2: TUBEROUS SCLEROSIS

S.NO	AGE	SEX	FH/O	AF	ASH	SHAG	KOENEN	CALM	CONFET	SZ	RSZ	ENAMEL	MR	DEL	LD	MICRO	EEG	CT	MRI		
																			TUBER	SEN	SEGA
1	11	M	2	1	1	1	2	2	1	1	1	1	2	2	1	2	N	2	P	A	A
2	12	F	2	1	1	1	2	2	1	1	1	1	2	2	2	2	N	2	P	A	A
3	15	M	1	1	1	1	1	1	2	1	1	1	1	1	1	1	AB	2	A	A	A
4	14	F	1	1	1	1	1	1	2	1	1	1	1	1	1	1	AB	2	A	A	A
5	34	F	2	1	1	1	1	1	2	1	1	1	1	2	1	2	AB	1	A	A	P
6	18	F	2	1	1	1	2	2	2	1	1	1	1	2	1	2	N	2	A	A	A
7	17	F	2	1	1	1	2	2	2	1	1	1	1	2	1	2	N	2	A	A	A
8	29	F	2	1	1	1	1	2	2	1	1	1	1	2	1	2	AB	2	A	P	A
9	28	F	2	1	1	1	1	2	2	1	1	1	1	2	1	2	AB	2	A	P	A
10	26	F	2	1	1	1	2	2	2	1	1	1	1	2	1	2	AB	2	A	P	A
11	11	F	2	1	1	1	2	2	2	1	1	2	2	2	2	2	N	2	P	A	A
12	13	M	2	1	1	1	2	2	2	1	1	2	2	2	2	2	N	2	A	A	A
13	16	F	2	1	1	2	2	2	2	1	2	2	2	2	2	2	N	2	A	A	A
14	6	F	2	1	1	1	2	2	2	1	2	2	2	2	2	2	N	2	A	A	A
15	9	F	2	1	1	1	2	2	2	1	2	2	2	2	2	2	N	2	A	A	A
16	7	M	2	1	1	2	2	2	2	2	2	2	2	2	2	2	N	2	A	A	A
17	26	M	2	1	2	2	2	2	2	2	2	2	2	2	2	2	N	2	A	A	A
18	38	M	2	1	2	2	2	2	2	2	2	2	2	2	2	2	N	2	A	A	A

MASTER CHART 3: OTHER NEURO CUTANEOUS SYNDROMES

S.NO	AGE	SEX	NC	F/H	PW	NAVE	SKIN	MR	SZ	WEAK	ATAXIA	HFA	EYE	MRI	EEG
1	13	F	SW	2	1	2	2	1	1	2	2	2	1	AB	AB
2	32	F	SW	2	1	2	2	2	2	2	2	2	1	N	N
3	18	M	SW	2	1	2	2	2	1	2	2	2	1	AB	AB
4	60	F	SW	2	1	2	2	2	1	2	2	2	1	AB	AB
5	13	M	AT	1	2	2	2	1	1	1	1	2	1	AB	AB
6	8	F	AT	1	2	2	2	2	2	2	1	2	1	AB	N
7	9	F	AT	2	2	2	2	2	2	2	1	2	1	AB	N
8	45	F	GM	2	2	1	2	2	2	2	2	2	2	N	N
9	31	M	GM	2	2	1	2	2	1	2	2	2	2	N	N
10	30	F	EN	2	2	1	2	2	2	2	2	2	2	N	N
11	35	M	EN	2	2	1	2	2	1	2	2	2	2	N	N
12	10	M	ITO	2	2	2	1	1	1	2	2	2	2	AB	N
13	11	F	XP	2	2	2	1	1	2	2	2	2	1	AB	N
14	28	M	ED	2	2	2	1	2	2	2	2	2	1	N	N
15	12	M	HHA	2	2	2	2	2	1	2	2	1	2	AB	AB
16	10months	F	IP	2	2	2	1	2	1	2	2	2	2	AB	AB

KEYS TO MASTER CHART

1	**:**	PRESENT
2	**:**	ABSENT
M	**:**	MALE
F	**:**	FEMALE
N	**:**	NORMAL
P	**:**	PRESENT
AB	**:**	ABNORMAL
FH	**:**	FAMILY HISTORY
AF	**:**	ANGIO FIBROMA
ASH	**:**	ASH LEFF MACCULE
ATAXIA	**:**	CEREBELLAR ATAXIA
BONY	**:**	SKELETAL ABNORMALITIES
CALM	**:**	CAFÉ AU LAIT
CONFET	**:**	CONFETTI LESIONS
CT	**:**	COMPUTARISED TOMOGRAPHY
DEL	**:**	DEVELOPMENT DELAY
ED	**:**	EHLER DANLOS SYNDROME
EEG	**:**	ELECTRO ENCEPHALOGRAPHY
EN	**:**	EPIDERMAL NAEVUS
ENAMEL	**:**	ENAMEL PITS
EYE	**:**	EYE ABNORMALITIES
FAT	**:**	HEMIFACIAL ATROPHY
FRC	**:**	FRECKLE
GM	**:**	GIANT MELANOCYTIC NAEVUS
HEAR	**:**	HEARING LOSS
HHA	**:**	HERIDITARY HEMIFACIAL ATROPHY
IP	**:**	INCONTINENTIA PIGMENTI

ITO	**:**	HYPOMELANOSIS OF ITO
KOENEN	**:**	KOENEN SUB UNGAL FIBROMA
LD	**:**	LEARNING DISABILITY
LISCH	**:**	LISCH NODULES
MICRO	**:**	MICROCEPHALY
MR	**:**	MENTAL RETARDATION
MRI	**:**	MAGNETIC RESONANCE IMAGE
NAVI	**:**	NAEVI
NC	**:**	NEUROCUTANEOUS SYNDROME
NF	**:**	NEURO FIBROMA
ONG	**:**	OPTIC NERVE GLICOMA
PARESIS	**:**	WEAKNESS OF LIMBS
PE	**:**	PAPILLEDEMA
PW	**:**	PORT WINE STAIN
PX	**:**	PLEXIFORM NEURO FIBROMA
REFSZ	**:**	INTRACTABLE SEIZURES
SEGA	**:**	SUBEPENDYMAL GIANT ALL ASTROCYTOMA
SHAG	**:**	SHAGREEN PATCH
SKIN	**:**	OTHER SKIN LESIONS
SW	**:**	STURGE WEBER SYNDROME
SZ	**:**	SEIZURES
TUBER	**:**	CORTICAL TUBERS
UBO	**:**	UNIDENTIFIED BRIGHT OBJECTS
XP	**:**	XERODERMA PIGMENTOSUM

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. T. Vijay
PG in DM Neurology
Madras Medical College, Chennai -3

Dear Dr. T. Vijay

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study on clinical and radiological features of neurocutaneous syndromes " No.36012012.

The following members of Ethics Committee were present in the meeting held on 27.01.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. Shruti Kamal MS Prof of Surgery, Madras Medical College , Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

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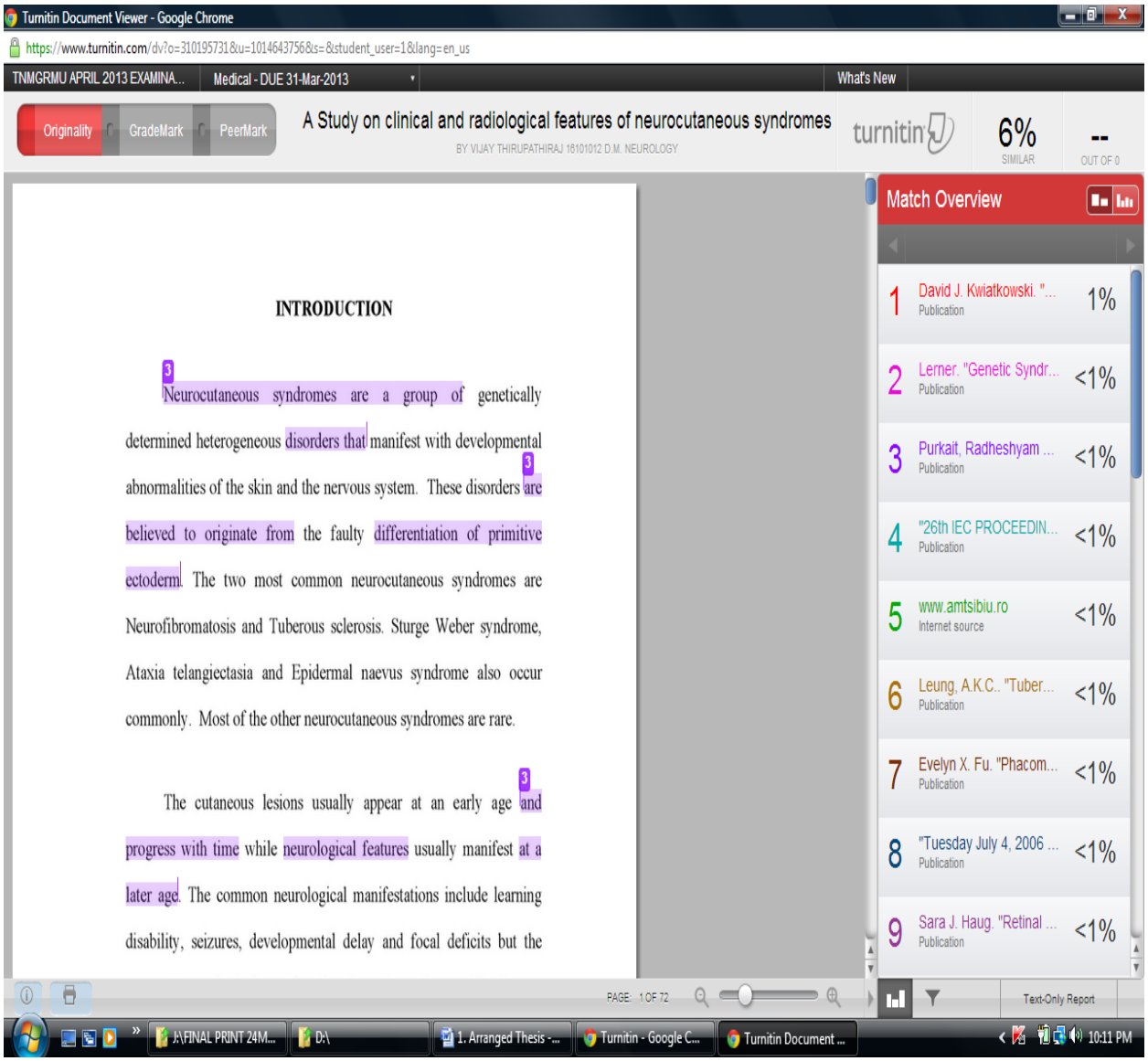
Assignment title	Medical
Author	Vijay Thirupathiraj 16101012 D.M. Neurology
E-mail	majortvijaysow@gmail.com
Submission time	24-Mar-2013 10:09PM
Total words	9294

First 100 words of your submission

INTRODUCTION Neurocutaneous syndromes are a group of genetically determined heterogeneous disorders that manifest with developmental abnormalities of the skin and the nervous system. These disorders are believed to originate from the faulty differentiation of primitive ectoderm. The two most common neurocutaneous syndromes are Neurofibromatosis and Tuberous sclerosis. Sturge Weber syndrome, Ataxia telangiectasia and Epidermal naevus syndrome also occur commonly. Most of the other neurocutaneous syndromes are rare. The cutaneous lesions usually appear at an early age and progress with time while neurological features usually manifest at a later age. The common neurological manifestations...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INTRODUCTION
Neurocutaneous syndromes are a group of genetically determined heterogeneous disorders that manifest with developmental abnormalities of the skin and the nervous system. These disorders are believed to originate from the faulty differentiation of primitive ectoderm. The two most common neurocutaneous syndromes are Neurofibromatosis and Tuberous sclerosis. Sturge Weber syndrome, Ataxia telangiectasia and Epidermal naevus syndrome also occur commonly. Most of the other neurocutaneous syndromes are rare.
The cutaneous lesions usually appear at an early age and progress with time while neurological features usually manifest at a later age. The common neurological manifestations include learning disability, seizures, developmental delay and focal deficits but the
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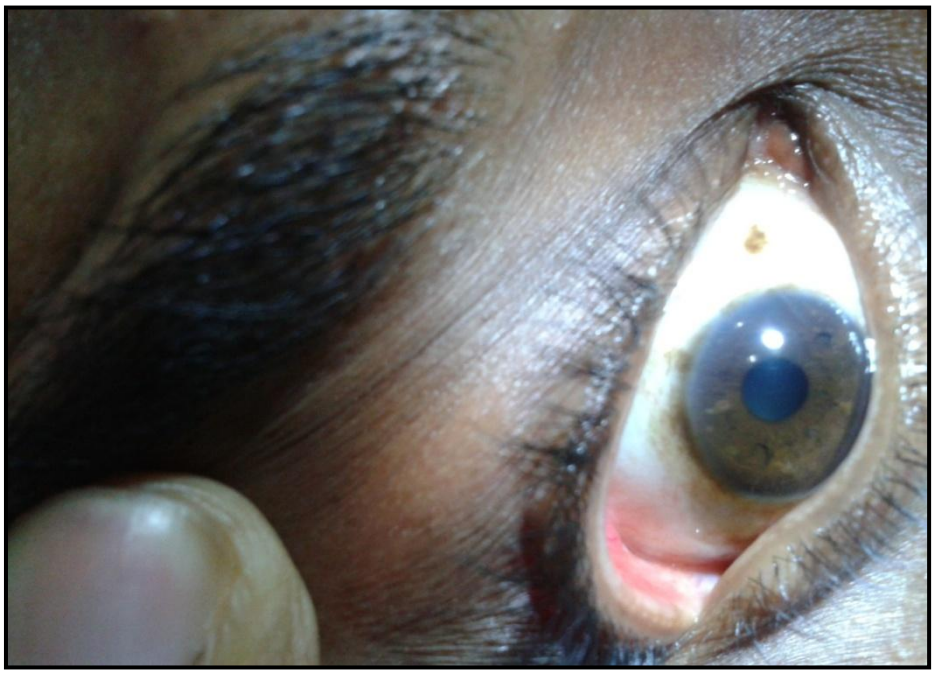
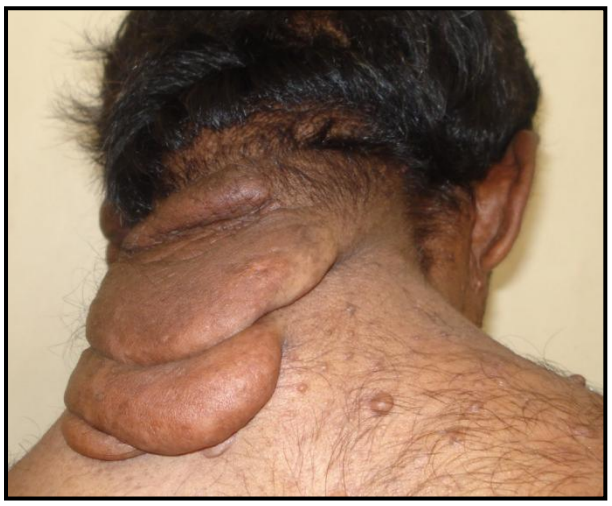
NEURO FIBROMATOSIS

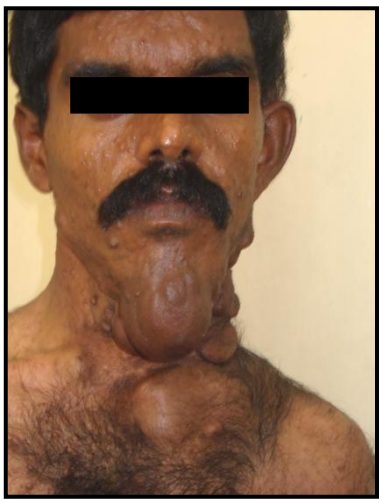
Café au lait macules



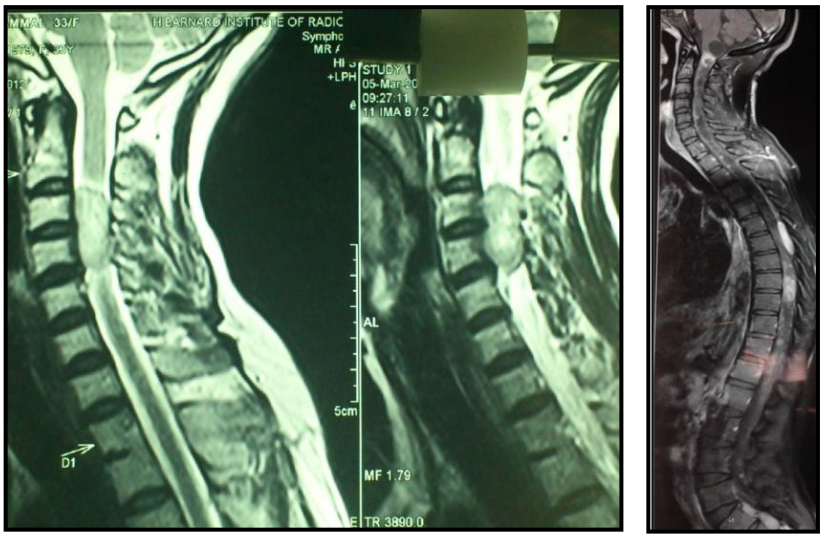
Lisch nodules

PLEXIFORM NEURO FIBROMAS

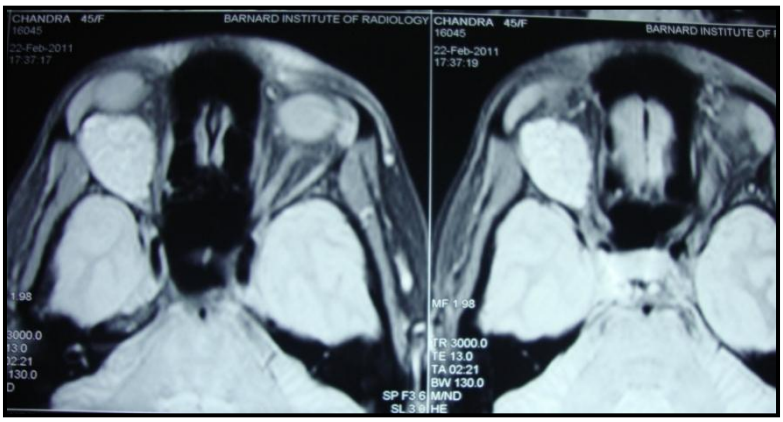




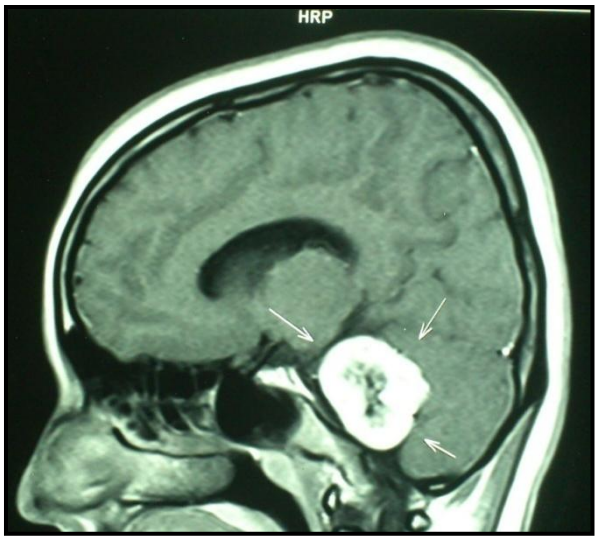
NEUROIMAGING IN NEUROFIBROMATOSIS



Spinal cord compression



Optic nerve glioma



Acoustic Schawanoma

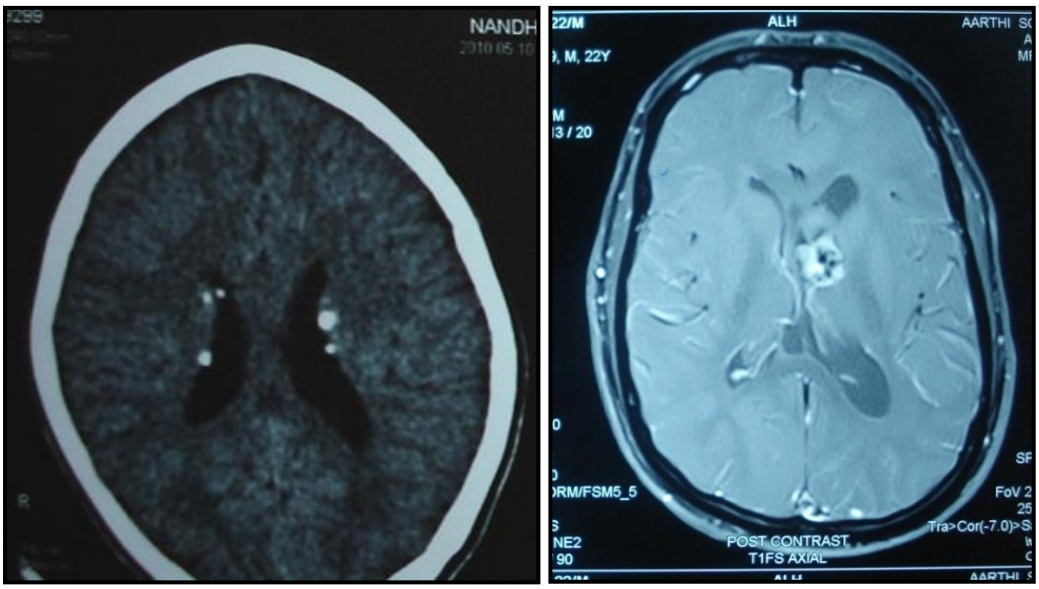
TUBEROUS SCLEROSIS

ASH LEAF MACULE IN TSC

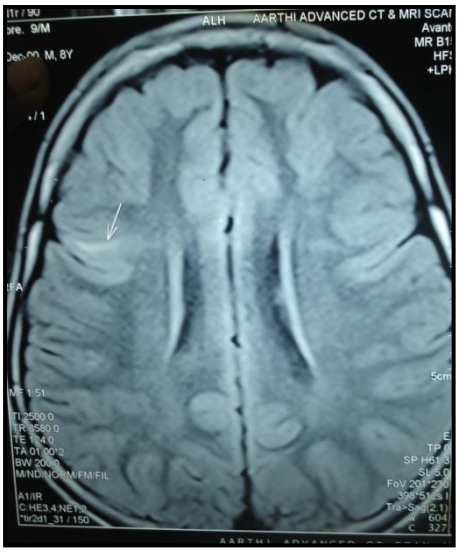
SHAGREEN PATCH IN TSC

ADENOMA SABECUM

IMAGING IN TUBEROUS SCLEROSIS



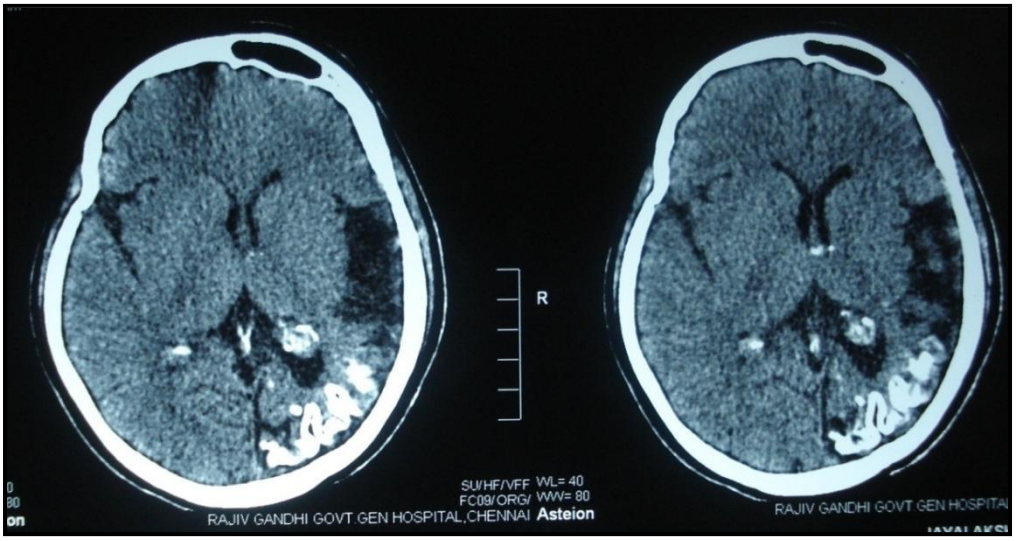
SUB EPENDDYMAL NODULES



CORTICAL TUBER

STURGE WEBER SYNDROME

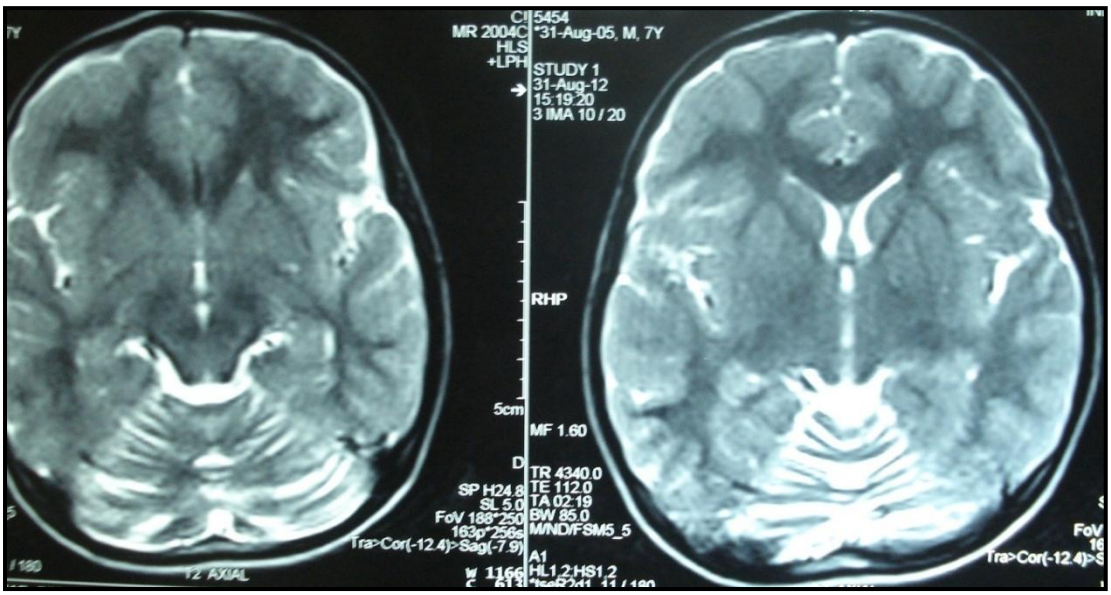
Port wine stain



Pariet occiptal Calcifications and atrophy

ATAXIA TELANGIECTASIA

Conjuctival Telangiectasia



Cerebellar Atrophy

XERODERMA PIGMENTOSA

Incontinentia Pigmenti

Epidermal Naevus Syndrome

PARRY ROMBERG SYNDROME-IMAGING

Hemifacial atrophy with ipsilateral hemispheric atrophy

Introduction

Aim of the Study

Review of Literature

Materials and Methods

Observation and Results

Discussion

Conclusion

Bibliography

Annexures